

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 May 2003 (15.05.2003)

PCT

(10) International Publication Number
WO 03/040107 A1

(51) International Patent Classification⁷: C07D 233/90,
401/04, 405/04, 409/04, 413/04, A61K 31/415, A61P 3/04

(21) International Application Number: PCT/US02/30545

(22) International Filing Date:
24 September 2002 (24.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/324,473 24 September 2001 (24.09.2001) US

(71) Applicant (for all designated States except US): BAYER
PHARMACEUTICALS CORPORATION [US/US];
400 Morgan Lane, West Haven, CT 06516 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): SMITH, Roger,
A. [US/US]; 65 Winterhill Road, Madison, CT 06443
(US). O'CONNOR, Stephen, J. [US/US]; 977 Little
Meadow Road, Guilford, CT 06437 (US). WIRTZ,
Stephan-Nicholas [DE/DE]; Briller Strasse 40, 42105
Wuppertal (DE). WONG, Wai, C. [US/US]; 314 Aspen
Glen Drive, Hamden, CT 06518 (US). CHOI, Soongyu
[KR/US]; 44 Jamestown Road, Trumbull, CT 06611 (US).
KLUENDER, Harold, C. E. [US/US]; 27 Academy
Road, Trumbull, CT 06611 (US). SU, Ning [CN/US]; 121
October Hill Road, Hamden, CT 06518 (US). WANG,
Gan [CN/US]; 5 Cassella Drive, Wallingford, CT 06492
(US). ACHEBE, Furahi [US/US]; 10 Woodland Street,
West Haven, CT 06516 (US). YING, Shihong [CN/US];
280 Bittersweet Road, Orange, CT 06477 (US).

(74) Agents: GREENMAN, Jeffrey, M. et al.; Bayer Pharma-
ceuticals Corporation, 400 Morgan Lane, West Haven, CT
06516 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, EE, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

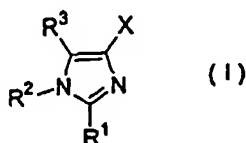
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZOLE-4-CARBOXAMIDE DERIVATIVES, PREPARATION AND USE THEREOF FOR TREATMENT OF OBESITY



(57) Abstract: This invention relates to substituted imidazole derivatives of formula I, which have been found to suppress appetite and induce weight loss. The invention also provides methods for synthesis of the compounds, pharmaceutical compositions comprising the compounds, and methods of using such compositions for inducing weight loss and treating obesity and obesity-related disorders.

IMIDAZOLE-4-CARBOXAMIDE DERIVATIVES, PREPARATION AND USE THEREOF FOR TREATMENT OF OBESITY

This application claims benefit of U.S. Provisional Application Serial No. 60/324,473, filed September 24, 2001, the contents of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to the field of pharmaceuticals, in particular to the field of obesity treatment. More specifically, it relates to certain imidazole compounds which are useful in the treatment of obesity and obesity-related disorders, and as weight-loss and weight-control agents.

BACKGROUND OF THE INVENTION

Obesity, which is defined as an excess of body fat relative to lean body mass, is a well-established risk factor for a number of potentially life-threatening diseases such as atherosclerosis, hypertension, diabetes, stroke, pulmonary embolism, sleep apnea, and cancer. Furthermore, it complicates numerous chronic conditions such as respiratory diseases, osteoarthritis, osteoporosis, gall bladder disease, and dyslipidemias. The enormity of this problem is best reflected in the fact that death rates escalate with increasing body weight. More than 50% of all-cause mortality is attributable to obesity-related conditions once the body mass index (BMI) exceeds 30 kg/m², as seen in 35 million Americans (Lee, JAMA 268:2045-2049, 1992). By contributing to greater than 300,000 deaths per year, obesity ranks second only to tobacco smoking as the most common cause of potentially preventable death (McGinnis, JAMA 270:2207-2212, 1993). Accompanying the devastating medical consequences of this problem is the severe financial burden placed on the health care system in the United States. It is estimated that 30-50% of the middle-age population may be considered as obese (Kuczmarski et al., JAMA 272:205-211, 1994). The economic impact of obesity and its associated illnesses from medical expenses and loss of income are reported to be in excess of \$68 billion/a year (Colditz, Am. J. Clin. Nutr. 55:503S-507S, 1992). This figure does not include the greater than \$30 billion per year spent on weight loss foods, products, and programs (Wolf, Pharmacoeconomics. 5:34-37, 1994).

The accumulation or maintenance of body fat bears a direct relationship to caloric intake. Comprehensive treatment programs, therefore, focused on behavior modifications to reduce caloric intake and increase physical activity using a myriad of systems. These methods have limited efficacy and are associated with recidivism rates exceeding 95% (NIH Technology Assessment Conference Panel, Ann. Intern. Med. 119:764-770, 1993).

Obesity has also been treated by administering specific agents, for example, anorectic agents, to obese subjects. However, anorectic agents such as dextroamphetamine, the combination of the non-amphetamine drugs phentermine and fenfluramine (Phen-Fen), and dexfenfluramine

(Redux) alone, are associated with serious side effects. Indigestible materials such as olestra (OLEAN[®], mineral oil or neopentyl esters (see U.S. Pat. No. 2,962,419)) have been proposed as substitutes for dietary fat. Garcinia acid and derivatives thereof have been described as treating obesity by interfering with fatty acid synthesis. Swellable crosslinked vinyl pyridine resins have been described as appetite suppressants via the mechanism of providing non-nutritive bulk (see, e.g., U.S. Pat. No. 2,923,662).

Surgical interventions, such as gastric partitioning procedures, jejunoileal bypass, and vagotomy, have also been developed to treat severe obesity (Greenway, Endo. Metab. Clin. N. Amer. 25:1005-1027, 1996). Although these surgical procedures are somewhat more effective in the long run, the acute risk benefit ratio has reserved these invasive procedures for morbidly obese patients according to the National Health Institutes (NIH) consensus conference on obesity surgery (BMI>40 kg/m²) (NIH Conference, Ann. Intern. Med. 115:956-961, 1991). Therefore, this approach is not an alternative for the majority of overweight patients unless and until they become profoundly obese and are suffering the attendant complications.

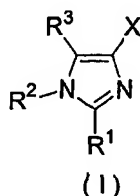
Thus, new methods and compositions that promote weight-loss are urgently needed.

SUMMARY OF THE INVENTION

The present invention provides substituted imidazole derivatives which have been found to suppress appetite and induce weight loss in laboratory animals. The invention also provides methods for synthesis of the compounds, pharmaceutical compositions comprising the compounds, and methods of using such compositions for inducing weight loss and treating obesity and obesity-related disorders.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to substituted imidazole derivatives that have utility in the treatment of obesity, said derivatives having Formula I



wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, (C₁-C₆)alkyl sulfonyl, (C₁-C₆)alkyl sulfonyl-amino, (C₁-C₆)alkyl carbonyl-amino, (C₁-C₆)alkyl amino-carbonyl-amino, or phenyl,

5 (C₂-C₆)alkyl,

cyclohexyl optionally substituted with (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or with one or more fluorine,

10 1-naphthyl or 2-naphthyl optionally substituted with halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano,

benzyl optionally substituted on the phenyl ring with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano,

15

a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with fluorine, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano, and

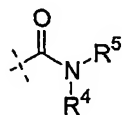
20

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or phenyl;

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;

25

X is



where R⁴ is hydrogen or (C₁-C₆)alkyl;

R⁵ is selected from

30

(C₂-C₉)alkyl or (C₇-C₁₁)bicycloalkyl, each of which may optionally be substituted with one or more phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-amino, bis[(C₁-C₃)alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, 2,3-dihydro-1,4-benzodioxin-2-yl, hydroxy-substituted (C₁-C₆)alkyl, or fluorine,

benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy (C₁-C₆)alkyl, and optionally substituted on the phenyl ring with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, or nitro,

piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with (C₁-C₆)alkyl, hydroxy-substituted (C₁-C₆)alkyl, (C₁-C₃)alkoxy-substituted (C₁-C₃)alkyl, benzyl, or phenyl optionally substituted with one or more of (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or halogen,

-NR⁶R⁷

where R⁶ is hydrogen or (C₁-C₆)alkyl;

R⁷ is (C₁-C₉)alkyl; or phenyl optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy-substituted (C₁-C₆)alkyl, (C₁-C₃)alkoxy-substituted (C₁-C₃)alkyl, phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom, or

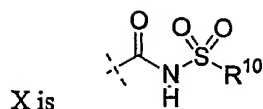
R⁶ and R⁷, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more (C₁-C₆)alkyl, (C₁-C₆)alkoxy, hydroxy-substituted (C₁-C₃)alkyl, (C₁-C₃)alkoxy-substituted (C₁-C₃)alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

or

R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of fluorine, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-amino, bis[(C₁-C₃)alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C₁-C₆)alkyl, phenyl-substituted (C₁-C₆)alkyl, cyano, a 5- to 10-

membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more (C₁-C₆)alkyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

5 or



10 where R¹⁰ is (C₁-C₉)alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, or a fluorine atom, or

phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, or halogen;

15

and pharmaceutical salts and esters thereof.

Another embodiment of the invention consists of imidazole derivatives having Formula I wherein

20 R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, (C₁-C₆)alkyl carbonyl-amino, (C₁-C₆)alkyl amino-carbonyl-amino, or phenyl,

25

(C₂-C₆)alkyl,

cyclohexyl optionally substituted with (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or with one or more fluorine,

30

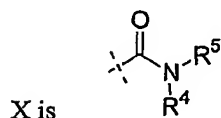
1- or 2-naphthyl optionally substituted with halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano,

benzyl optionally substituted on the phenyl ring with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano,

a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with fluorine, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano, and

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or phenyl, with the proviso that R² is not an unsubstituted 4-pyridyl or an unsubstituted 4-pyrimidinyl group;

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;

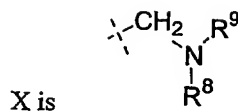


where R⁴ is hydrogen or (C₁-C₆)alkyl;

R⁵ is phenyl substituted with one or more (C₁-C₆)alkyl, hydroxy (C₁-C₆)alkyl, (C₁-C₆)alkoxy, phenyl, hydroxy, benzyloxy, trifluoromethyl, or halogen, or

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or trifluoromethyl;

or



where R⁸ is a hydrogen or (C₁-C₆)alkyl;

R^9 is a (C₁-C₉)alkyl or (C₇-C₁₁)bicycloalkyl group, each of which is optionally substituted with one or more of phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, or fluorine,

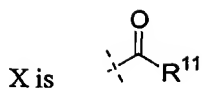
benzyl in which the phenyl ring is optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen, or

phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, or halogen;

or

R^8 and R^9 , together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of (C₁-C₆)alkyl, benzyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, halogen, a 5- to 10-membered saturated or unsaturated heterocyclic radical; or phenyl optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

or



where R^{11} is (C₂-C₉)alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, or fluorine,

phenyl in which the phenyl ring is optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen,

benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which may be optionally substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy (C₁-C₆)alkyl, and optionally substituted on the phenyl ring with halogen,

(C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy or nitro,
or

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical;

and pharmaceutical salts and esters thereof.

The terms identified above have the following meaning throughout:

“Halogen” means fluorine, chlorine, bromine or iodine.

The terms “(C₁-C₃)alkyl”, “(C₁-C₆)alkyl”, “(C₂-C₆)alkyl”, “(C₁-C₉)alkyl”, and “(C₂-C₉)alkyl” mean C₁-C₃, C₁-C₆, C₂-C₆, C₁-C₉, and C₂-C₉ linear or branched alkyl groups, respectively, that may also include a cyclic alkyl radical as part of the alkyl group. For example, this includes groups such as cyclopropyl, cyclohexyl, cyclopropyl-methyl, and cycloheptyl-methyl groups. The preferred alkyl groups are methyl, ethyl, propyl, and isopropyl groups.

“(C₁-C₃)alkoxy” and “(C₁-C₆)alkoxy” mean (C₁-C₃)alkyl-oxy and (C₁-C₆)alkyl-oxy, respectively.

“(C₇-C₁₁)bicycloalkyl” means a C₇-C₁₁ bicyclic alkyl group, such as octahydro-2-pentalenyl, bicyclo[2.2.1]hept-2-yl, and bicyclo[3.2.1]oct-8-yl, that is optionally substituted with one or more methyl groups.

The term “5- to 10-membered saturated or unsaturated heterocyclic radical” means a fused or bridged, mono-, bi-, or tri-cyclic, non-aromatic heterocyclic radical which may contain one to three of the heteroatoms nitrogen, oxygen, or sulfur. These radicals include the following radicals, for example, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, azepan-1-yl, morpholin-4-yl, hexahydrocyclopenta[c]pyrrol-2(1H)-yl, and thiomorpholin-4-yl.

The term “5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical” means a 5- or 6-membered aromatic heterocyclic radical or a fused bicyclic aromatic heterocyclic radical, which may contain one to three of the heteroatoms nitrogen, oxygen, or sulfur. These radicals include the following radicals, for example, furyl, thienyl, isoxazolyl, pyridyl, pyrimidinyl, benzofuranyl, and benzothienyl.

When any moiety is described as being substituted, it can have one or more of the indicated substituents that can be located at any available position on the moiety. When there are two or more substituents on any moiety, each term shall be defined independently of any other in each occurrence.

Representative salts of the compounds of Formula I include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic

acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine salts and *N*-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

The esters in the present invention are non-toxic, pharmaceutically acceptable ester derivatives of the alcohols of Formula I. This includes ester derivatives prepared from acetic, benzoic, mandelic, stearic, lactic, salicylic, hydroxynaphthoic, glucoheptonic, and gluconic acid. The alcohol compounds of Formula I may be esterified by a variety of conventional procedures including reacting the appropriate anhydride, carboxylic acid, or acid chloride with the alcohol group of the Formula I compound. The appropriate anhydride is reacted with the alcohol in the presence of an acylation catalyst such as 1,8-bis(dimethylamino)naphthalene or DMAP (*N,N*-dimethylaminopyridine). An appropriate carboxylic acid may be reacted with the alcohol in the presence of a dehydrating agent such as dicyclohexylcarbodiimide, 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide or other water soluble dehydrating agents which are used to drive the reaction by the removal of water, and optionally, an acylation catalyst. Esterification may also be reached using the appropriate carboxylic acid in the presence of trifluoroacetic anhydride and optionally, pyridine, or in the presence of *N,N*-carbonyldiimidazole with pyridine. Reaction of an acid chloride with the alcohol may be carried out with an acylation catalyst such as DMAP or pyridine. One skilled in the art would readily know how to successfully carry out these as well as other methods of esterification of alcohols. Sensitive or reactive groups on the compound of Formula I may need to be protected during any of the above methods for forming esters, and protecting groups may be added and removed by conventional methods well known in the art.

It will be appreciated that diastereomers and enantiomers of the exemplified structures will often be possible, and that pure isomers represent preferred embodiments. It is intended that pure stereoisomers, and mixtures thereof, are within the scope of the invention.

The compounds of this invention may, either by nature of asymmetric centers or by restricted rotation, be present in the form of isomers. Any isomer may be present in the (*R*)-, (*S*)-, or (*R,S*) configuration, preferably in the (*R*)- or (*S*)- configuration, whichever is most active.

All isomers, whether separated, pure, partially pure, or in racemic mixture, of the compounds of this invention are encompassed within the scope of this invention. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art.

Geometric isomers by nature of substituents about a double bond or a ring may be present in *cis* (= *Z*-) or *trans* (= *E*-) form, and both isomeric forms are encompassed within the scope of this invention.

The particular process to be utilized in the preparation of the compounds of this invention depends upon the specific compound desired. Such factors as the selection of the specific moieties and the specific substituents on the various moieties, all play a role in the path to be followed in the preparation of the specific compounds of this invention. These factors are readily recognized by one of ordinary skill in the art.

For synthesis of any particular compound, one skilled in the art will recognize that the use of protecting groups may be required for the synthesis of compounds containing certain substituents. A description of suitable protecting groups and appropriate methods of adding and removing such groups may be found in: *Protective Groups in Organic Synthesis*, Second Edition, T. W. Greene, John Wiley and Sons, New York, 1991.

In the Reaction Schemes below, one skilled in the art will recognize that reagents and solvents actually used may be selected from several reagents and solvents well known in the art to be effective equivalents. When specific reagents or solvents are shown in a Reaction Scheme, therefore, they are meant to be illustrative examples of conditions desirable for the execution of that particular Reaction Scheme. Abbreviations not identified in accompanying text are listed later in this disclosure under "Abbreviations and Acronyms."

Another object of this invention is to provide methods of making the compounds of the invention. The compounds may be prepared from readily available materials by the methods outlined in Reaction Schemes 1 and 2 below, and by obvious modifications thereto.

The present invention relates to the use of the compounds of this invention for the treatment of bulimia and obesity including associated dyslipidemia and other obesity- and overweight-related complications such as, for example, cholesterol gallstones, cancer (e.g., colon,

rectum, prostate, breast, ovary, endometrium, cervix, gallbladder, and bile duct), menstrual abnormalities, infertility, polycystic ovaries, osteoarthritis, and sleep apnea, as well as for a number of other pharmaceutical uses associated therewith, such as the regulation of appetite and food intake, dyslipidemia, hypertriglyceridemia, Syndrome X, type II diabetes (non-insulin-
5 dependent diabetes), atherosclerotic diseases such as heart failure, hyperlipidemia, hypercholesterolemia, low HDL levels, hypertension, cardiovascular disease (including atherosclerosis, coronary heart disease, coronary artery disease, and hypertension), cerebrovascular disease and peripheral vessel disease. The compounds of this invention may also be useful for treating physiological disorders related to, for example, regulation of insulin sensitivity,
10 inflammatory response, plasma triglycerides, HDL, LDL and cholesterol levels and the like.

The compounds of Formula I of this invention are expected to be valuable as therapeutic agents. Accordingly, an embodiment of this invention includes a method of treating the various conditions identified above in a patient (including mammals) which comprises administering to said patient a composition containing an amount of the compound of Formula I that is effective in
15 treating the target condition.

Compounds of Formula I may be administered alone or in combination with one or more additional therapeutic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of Formula I and one or more additional therapeutic agents, as well as administration of the compound of Formula I and each
20 additional therapeutic agents in its own separate pharmaceutical dosage formulation. For example, a compound of Formula I and a therapeutic agent may be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent may be administered in separate oral dosage formulations.

Where separate dosage formulations are used, the compound of Formula I and one or more
25 additional therapeutic agents may be administered at essentially the same time (e.g., concurrently) or at separately staggered times (e.g., sequentially).

For example, the compounds of Formula I may be used in combination with other therapies and drugs useful for the treatment of obesity, for example, in combination with β_3 -adrenoreceptor agonists such as CL-316,243, or in combination with a drug compound that
30 modulates digestion and/or metabolism such as drugs that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

In addition, the compounds of Formula I may be administered in combination with one or more of the following hypoglycemic agents for the treatment of diabetes or diabetes-related disorders: insulin; biguanidines such as metformin or buformin; sulfonylureas such as
35 acetohexamide, chloropropamide, tolazamide, tolbutamide, glyburide, glipizide, glyclazide; or any

other insulin secretagogue such as, for example, repaglinide and nateglinide; or α -glycosidase inhibitors such as acarbose, voglibose, or miglitol. Also, the compounds of Formula I may be used in combination with HMG Co-A reductase inhibitors (statins), bile acid binding resin, or fibric acid derivatives to improve the lipid profile of subjects with dyslipidemia. Compounds of Formula I may also be used in combination with agents that regulate hypertension (e.g., inhibitors of angiotension converting enzyme (ACE), β -blockers, calcium channel blockers).

Furthermore, compounds of the present invention were determined, following oral dosing in rodents, to be present in significant concentrations in the brain. Therefore, the compounds of this invention may have utility for the treatment of any of various CNS (central nervous system) or psychological disorders, such as the treatment of substance or behavioral addiction, and the treatment of disorders associated with the use of psychotropic substances. Likewise, the compounds of this invention may have utility for the management and treatment of cognition and memory disorders.

The compounds of Formula I may also be utilized, in free base form or in compositions, as well as in research and diagnostics or as analytical reference standards, and the like, which are well known in the art. Therefore, the present invention includes compositions which are comprised of an inert carrier and an effective amount of a compound of Formula I, or a salt, or ester thereof. An inert carrier is any material which does not interact with the compound to be carried and which lends support, means of conveyance, bulk, traceable material, and the like to the compound to be carried. An effective amount of the compound is that amount which produces a result or exerts an influence on the particular procedure being performed.

It is anticipated that prodrug forms of the compounds of this invention will prove useful in certain circumstances, and such compounds are also intended to fall within the scope of the invention. Prodrug forms may have advantages over the parent compounds exemplified herein, in that they are better absorbed, better distributed, more readily penetrate the central nervous system, are more slowly metabolized or cleared, etc. Prodrug forms may also have formulation advantages in terms of crystallinity or water solubility. For example, compounds of the invention having one or more hydroxyl groups may be converted to esters or carbonates bearing one or more carboxyl, hydroxyl or amino groups, which are hydrolyzed at physiological pH values or are cleaved by endogenous esterases or lipases *in vivo*. See for example U.S. Patent Nos. 4,942,184; 4,960,790; 5,817,840; and 5,824,701 (all of which are incorporated herein by reference in their entirety), and references therein.

An object of this invention is to provide a method of inducing weight loss in an individual by administration of a compound of the invention. The method of the invention comprises administering to an individual a therapeutically effective amount of at least one compound of the

invention, or a prodrug thereof, which is sufficient to induce weight loss. The invention further comprises a method of preventing weight gain in an individual by administering an amount of at least one compound of the invention, or a prodrug thereof, which is sufficient to prevent weight gain.

5

General Preparation of Compounds of Formula I

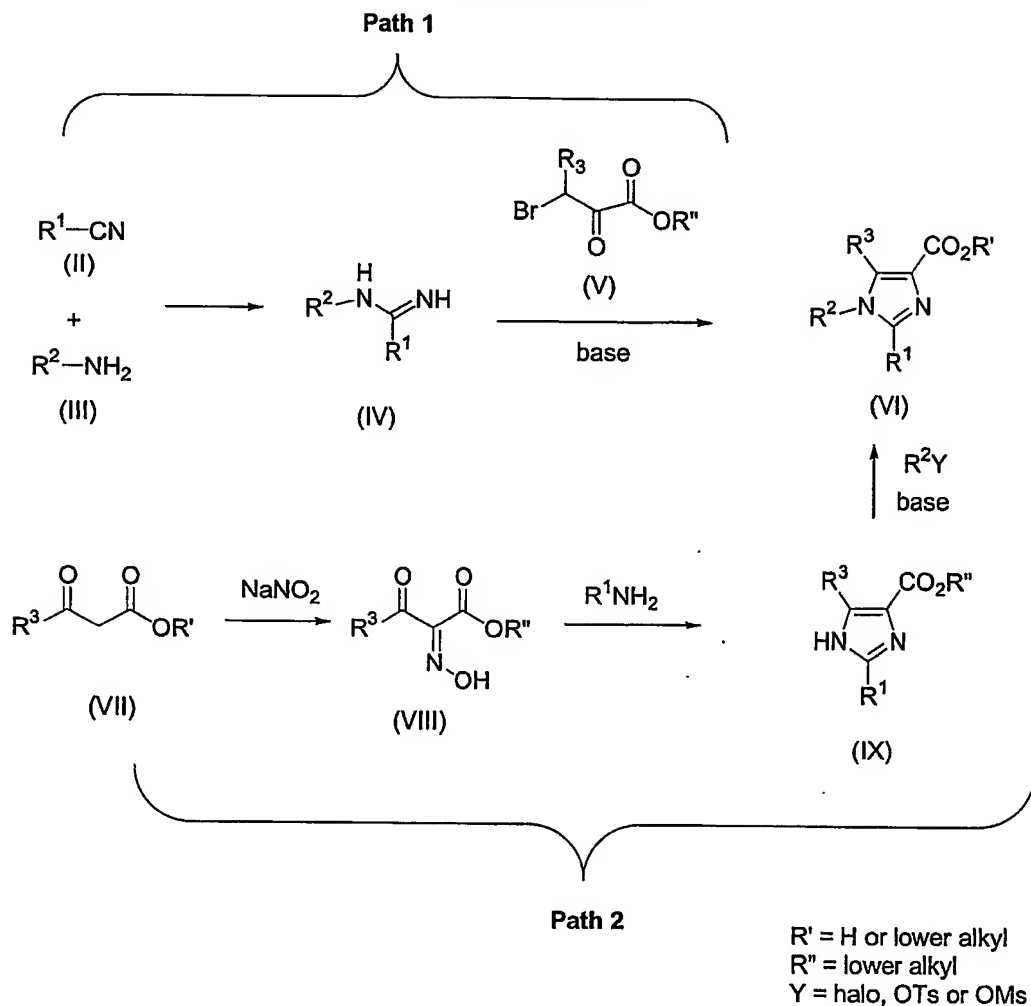
Compounds of Formula I are prepared by a variety of methodologies. The selection of the particular method to be used depends upon such factors as the availability of appropriate starting materials, compatibility of functional groups with the reagents used, and the ultimate structural features present in the final compound being prepared. It will be understood by those skilled in the art that more than one method may, in some cases, be useful for the preparation of individual compound examples of Formula I.

10

In general, the compounds of Formula I are prepared from the intermediate compound of Formula VI by the methods outlined in Reaction Scheme 2; the compound of formula VI is prepared by the methods outlined in Reaction Scheme 1, by one of the two paths as shown. For the compounds of Formulas Ia-d and II-XIII, unless specifically defined otherwise, R, R¹-R¹¹, and X are as defined above for Formula I.

15

Reaction Scheme 1

Preparation of Intermediates of Formula VI (Reaction Scheme 1)

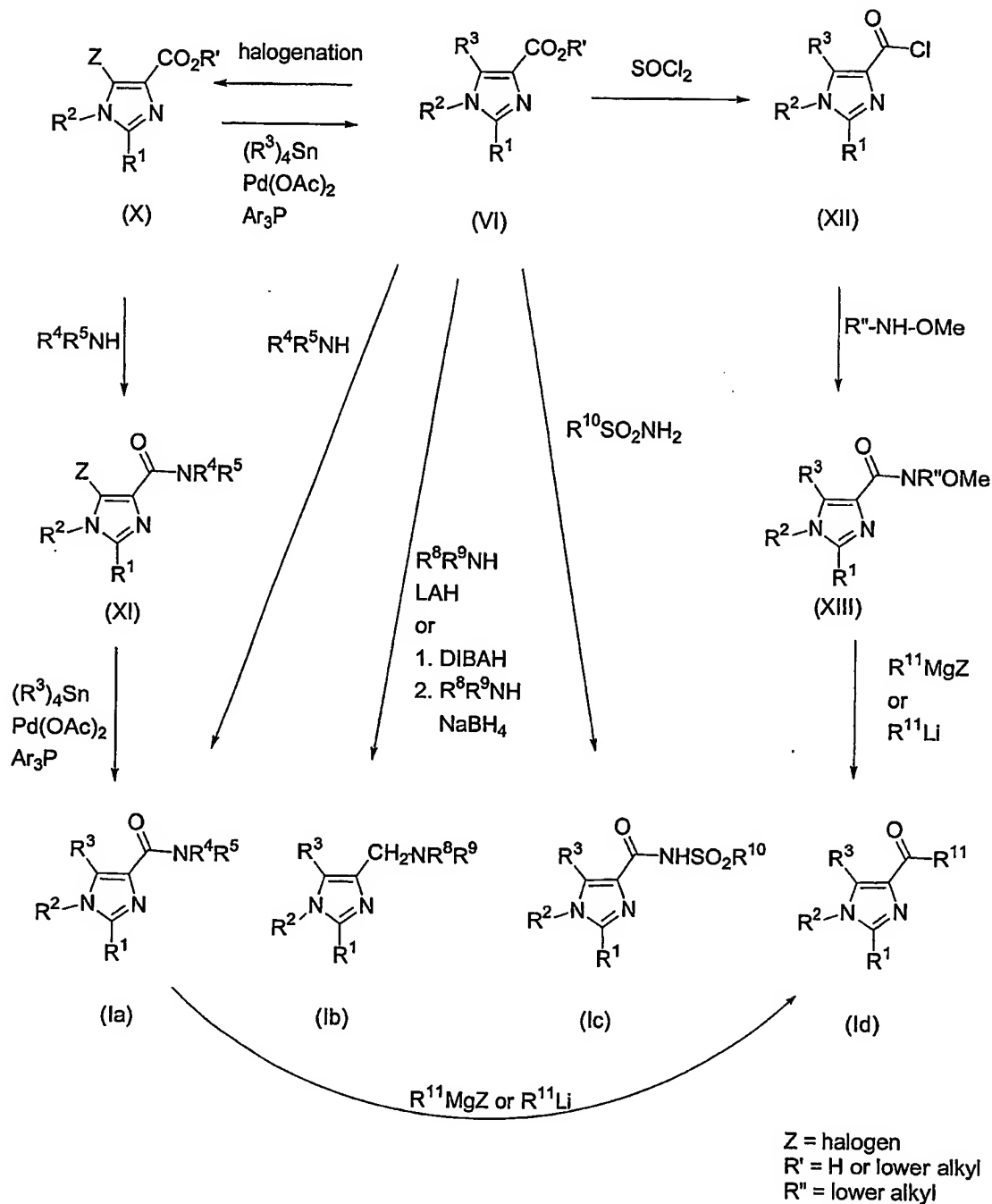
- 5 In Path 1, an imidamide of Formula IV is prepared by reaction of an amine of Formula III with a nitrile of Formula II. This reaction is either conducted using a strong base such as a Grignard reagent (e.g., EtMgBr) in a neutral solvent (e.g., THF) at room temperature, or with a Lewis Acid (e.g., AlCl_3) in an inert solvent (e.g., toluene) with heating. The product, imidamide IV, is then allowed to react with a 3-bromopyruvate of Formula V by mixing together in an inert solvent (e.g., toluene or THF), with optional heating, to give the imidazole intermediate of Formula VI. This reaction may be further facilitated by the addition of a base (e.g., propyl amine, sodium carbonate, and the like) to remove excess HBr produced as a side product. Alternatively, the conversion of IV to VI may be accomplished in a stepwise manner, i.e., first carrying out the
- 10

reaction of IV with V and isolation of the crude product, and then heating the residue with the R^1NH_2 compound in acetic acid complete the cyclization to imidazole VI.

In path 2, ketoesters of Formula VII are converted to an oxime compound of Formula VIII, by reaction with sodium nitrite in a protic solvent, typically acetic acid/water, while cooling.

5 The product VIII is then heated with an amine of formula R^1NH_2 in a polar solvent such as acetonitrile, to provide the imidazole of Formula IX. Finally, N-substitution may be carried out by treatment of IX with a base and a compound of formula R^2Y , where Y is a leaving group such as halogen, mesylate, or tosylate. For this pathway, when the R^2 is aryl, it is generally an activated (electrophilic) haloarene such as 4-halonitrobenzene or a 2- or 4-halopyridine, capable of
10 undergoing nucleophilic aromatic substitution reactions.

The compounds of Formula VI, in which R^1 is H, may be made from the compounds of Formula VI in which R^1 is alkyl, by ester hydrolysis methods well known in the art.

Reaction Scheme 2Preparation of Compounds of Formula I (Reaction Scheme 2)

5

The compounds of Formula VI, prepared as shown in Reaction Scheme 1, may then be used for the preparation of the compounds of Formula I. To illustrate the methods which are useful for the preparation of the Formula I compounds, synthetic routes are shown for the more

specific compounds of Formula Ia, Ib, Ic, and Id. These four structures represent the variants of the Formula I compounds when $X = -C(=O)NR^4R^5$, $-CH_2NR^8R^9$, $-C(=O)NHSO_2R^{10}$, and $-C(=O)R^{11}$, respectively.

5 The synthetic methods for the preparation of each of these variants of the Formula I compounds are illustrated in Reaction Scheme 2.

10 In one such method, compounds of Formula VI, in which $R' = H$, the carboxylic acid group is first activated as an acid halide (e.g., using $SOCl_2$ or TFFH) and subsequently treated with a compound of formula R^4R^5NH , usually with base present such as triethyl amine or PS-DIEA (polystyrene bound-diisopropylethylamine). Alternatively, the acid may be activated as a carbodiimide adduct (e.g., with 1-(3-dimethylaminopropyl, triethylamine, and 1-hydroxy-7-azabenzotriazole)-3-ethylcarbodiimide hydrochloride) or as a hexafluorophenyl ester (prepared from hexafluorophenol and EDCI). Following activation, a compound represented as R^4R^5NH is added to complete the reaction to the Formula Ia compound. One-pot variations of this conversion may also be carried out, for example, by mixing a coupling reagent such as HATU and the

15 R^4R^5NH compound at the same time.

Compounds of Formula Ia may also be prepared from compounds of Formula VI where $R' = \text{alkyl}$ by heating together the R^4R^5NH compound and trimethylaluminum.

20 Compounds of Formula Ia may also be prepared as shown, from an ester of Formula VI where R^3 is H, by first halogenating the imidazole by standard means (e.g., NBS or SO_2Cl_2) to give the haloimidazole of Formula X. While this intermediate may be used to prepare Formula VI intermediates where $R^3 \neq H$, using such methods as Pd-catalyzed organotin coupling reactions (e.g., when R^3 is methyl), Formula X compounds may also be converted to the amides of Formula XI under the same conditions described above for conversion of Formula VI compounds to Formula Ia. The resulting amide of Formula XI may then be converted to a Formula Ia

25 compound, where $R^3 \neq H$, by Pd-catalyzed organotin coupling reactions.

Formula Ib compounds may be prepared from Formula VI compounds in the presence of an amino compound of Formula R^8R^9NH under reductive conditions. When R^8 is hydrogen, a Formula VI compound where $R' = \text{alkyl}$, is first partially reduced to the aldehyde with, for example, diisobutylaluminum hydride (DIBAH), the R^8R^9NH compound is added to form an imine

30 intermediate in situ, which is then reduced with sodium borohydride. When $R^8 \neq H$, the reductive alkylation may be accomplished in one step with the R^8R^9NH compound and lithium aluminum hydride by using the procedure described by Khanna et al., (Synthesis 607-608, 1975).

The acylsulfonamides of Formula Ic may be prepared by reaction of the Formula VI compound (where $R' = H$) with a sulfonamide of Formula $R^{10}SO_2NH_2$, facilitated by a coupling

agent such as, for example, a *N,N'*-dialkyl carbodiimide such as *N,N'*-dicyclohexyl carbodiimide and a base such as, for example, DMAP.

Formula Id compounds may be prepared by conversion of an acid chloride represented by Formula XII, prepared as described above from VI (where R' = H) and SOCl₂, to an amide of Formula XIII, which is then allowed to undergo reaction with a organometallic reagent such as, for example, an alkyl or aryl Grignard reagent of Formula R¹¹MgBr, prepared by standard methods. The resulting product is the ketone of Formula Id. This Formula Id ketone may also be prepared by similar reaction of aryl- or alkyl lithium reagents, such as, for example, R¹¹Li, with Formula XIII, or certain Formula Ia amides where R⁴R⁵NH is 4-piperidone.

Conversion of the substituted compounds of Formula Ia, Ib, Ic, and Id to differently substituted Formula I compounds may be carried out using standard functional group conversion chemistry. For example, keto substituents may be reduced with reagents such as Na₂BH₄, to the corresponding hydroxy substituted compounds. Other such examples are 1) the conversion of nitrophenyl substituent to the corresponding aminophenyl substituent, and 2) O- or N-alkylation or acylation of OH or NH substituents to give the corresponding O- or N-alkyl or O- or N-acyl substituted compounds.

EXPERIMENTAL EXAMPLES

The following specific preparative examples are included as illustrations of preparation of specific compounds of the invention, and are not to be construed as limiting the scope of the invention in any way.

NMR methods:

Proton (¹H) nuclear magnetic resonance (NMR) spectra were measured with a General Electric GN-Omega 300 (300 MHz) spectrometer with either Me₄Si (δ 0.00) or residual protonated solvent (CHCl₃ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as reference standard. Carbon (¹³C) NMR spectra were measured with a General Electric GN-Omega 300 (75 MHz) spectrometer with solvent (CDCl₃ δ 77.0; d₃-MeOD; δ 49.0; d₆-DMSO δ 39.5) as reference standard.

LC-MS instrumentation:

(a) a Gilson HPLC system equipped with two Gilson 306 pumps, a Gilson 215 Autosampler, a Gilson diode array detector, a YMC Pro C-18 column (2 x 23mm, 120 Å), and a Micromass LCZ single quadrupole mass spectrometer with z-spray electrospray ionization. Spectra were scanned from 120-800 amu over 1.5 seconds. ELSD (Evaporative Light Scattering Detector) data was also acquired as an analog channel.

(b) a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source.

5

HPLC conditions. In the Examples and Tables provided below, LC-MS data are given with retention times (RT) determined by using one of the following methods:

Method 1. Eluents were A: 2% acetonitrile in water with 0.02% TFA, and B: 2% water in acetonitrile with 0.02% TFA. Elution conditions consisted of a flow rate of 1.0 mL/min with an initial hold at 10% B for 0.5 minutes, followed by gradient elution from 10% B to 95% B over 3.5 minutes, followed by a final hold at 95% B for 0.5 minutes. Total run time was 6.5 minutes.

10

Method 2. Eluents as above; elution at a flow rate of 1.5 mL/min with an initial hold at 10% B for 0.5 minutes, followed by gradient elution from 10% B to 90% B over 3.5 minutes, followed by a final hold at 90% B for 0.5 minutes. Total run time was 4.8 minutes.

15

Abbreviations and Acronyms

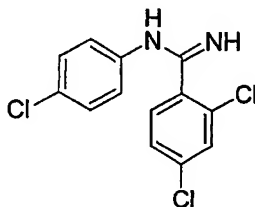
When the following abbreviations are used herein, they have the following meaning:

| | | |
|----|--------------------|--|
| | BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| | CD ₃ OD | methanol- <i>d</i> ₄ |
| 20 | Celite® | diatomaceous earth filter agent, ®Celite Corp. |
| | DMAP | 4-(<i>N,N</i> -dimethylamino)pyridine |
| | DMF | <i>N,N</i> -dimethylformamide |
| | DMSO | dimethylsulfoxide |
| | EDCI | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| 25 | ELSD | evaporative light scattering detector |
| | EtOAc | ethyl acetate |
| | EtOH | ethanol (100%) |
| | Et ₂ O | diethyl ether |
| | Et ₃ N | triethylamine |
| 30 | h | hour(s) |
| | HATU | <i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate |
| | HPLC | high performance liquid chromatography |
| | LC-MS | liquid chromatography-mass spectroscopy |
| 35 | min | minute(s) |

| | | |
|----|----------------|--|
| | m/z | mass-to-charge ratio |
| | MeCN | acetonitrile |
| | Ms | methanesulfonyl |
| | NBS | N- bromosuccinimide |
| 5 | NMM | 4-methylmorpholine |
| | OMs | methanesulfonyl-oxy |
| | OTs | 4-toluenesulfonyl-oxy |
| | PS-DIEA | Polystyrene-bound diisopropylethylamine |
| | R _f | retention factor (TLC) |
| 10 | RT | retention time (HPLC) |
| | rt | room temperature |
| | THF | tetrahydrofuran |
| | TFA | trifluoroacetic acid |
| | TFFH | Fluoro- <i>N,N,N',N'</i> -tetramethylformamidinium hexafluorophosphate |
| 15 | TLC | thin layer chromatography |
| | Ts | 4-toluenesulfonyl |

Example 1

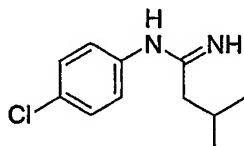
Preparation of 2,4-dichloro-*N*-(4-chlorophenyl)benzenecarboximidamide



Under argon, 4-chloroaniline (6.67 g, 52.5 mmol) was slowly added to EtMgBr (52 mL, 1 M in THF, 52 mmol) portion wise. After the solution was stirred for 0.5 h, 2,4-dichlorobenzonitrile (9.03 g, 52.5 mmol) was added. The resulting solution was stirred at rt overnight. The reaction mixture was carefully quenched with water and extracted with ethyl acetate. The organic layer was dried over MgSO₄, filtered, and concentrated. Crude product (16.26 g,) was obtained as a sticky brown foam which was used without purification for the next step. LC-MS *m/z* 299.3 (MH⁺), retention time 1.75 min (MDLC 1); ¹H NMR (300 MHz, CDCl₃) δ 4.92 (2H, br), 7.09-7.51 (7H, m).

Example 2

Preparation of *N*-(4-chlorophenyl)-3-methylbutanimidamide



5

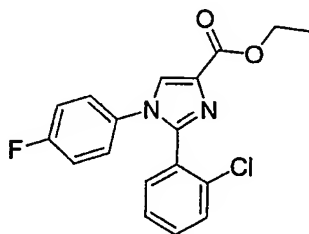
To a solution of 3-methylbutanenitrile (250 mg, 3.0 mmol) and AlCl_3 (400 mg, 3.0 mmol) in toluene (6 mL) was added 4-chloroaniline (383 mg, 3.0 mmol). The resulting solution was stirred at reflux for 2 h, diluted with water, and extracted with EtOAc. The aqueous layer was neutralized with saturated NaHCO_3 solution and extracted with EtOAc. The combined extracts were dried over MgSO_4 , filtered, and concentrated. The crude product (364 mg, 58% yield) was used for the next step without purification.

10

Example 3

Preparation of ethyl 1-(4-fluorophenyl)-2-(2-chlorophenyl)-1*H*-imidazole-4-carboxylate

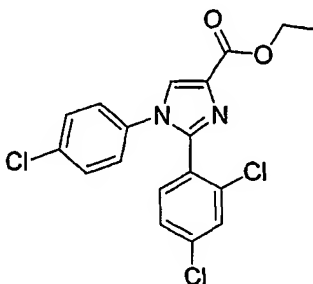
15



To a solution of crude 2-chloro-*N*-(4-fluorophenyl)benzenecarboximidamide (6.8 g, 27 mmol) in toluene (100 mL), ethyl bromopyruvate (3.5 mL, 27 mmol) was added. The resulting solution was heated at 115°C for 90 minutes. The reaction mixture was cooled to rt. Propylamine (2.2 mL, 27 mmol) was added. The reaction mixture was diluted with ethyl acetate and washed with saturated NaCl solution. The organic layer was dried over MgSO_4 , filtered, and concentrated. The residue was purified by flash chromatography over silica gel (30 % ethyl acetate in hexane) to give the product (3.4 g, 37% overall yield from 4-fluoroaniline) as a light yellow solid: LC-MS m/z 345.2 (MH^+), retention time 2.78 min (method 1); R_f = 0.20 (30% EtOAc in hexane). ^1H NMR (300 MHz, CDCl_3) δ 1.38-1.43 (3H, t, J = 6.9 Hz), 4.39-4.46 (2H, q, J = 3.9 Hz), 6.98-7.52 (8H, m), 7.89 (1H, s).

20

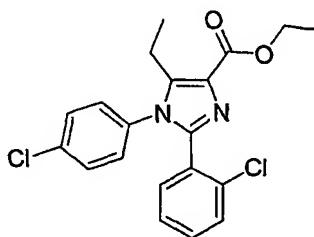
25

Example 4Preparation of ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxylate

5

To a solution of crude 2,4-dichloro-*N*-(4-chlorophenyl)benzenecarboximidamide (10.3 g, 34.6 mmol) in toluene (100 mL), ethyl bromopyruvate (4.3 mL, 34.6 mmol) and Na₂CO₃ (7.3 g, 41.6 mmol) were added. The resulting solution was heated at reflux for 3 h. The reaction mixture was cooled to rt. The solid was filtered off and the solvent was evaporated. The residue was purified by flash chromatography over silica gel (40 % ethyl acetate in hexane) to give the product (7.5 g, 52% overall yield from 4-chloroaniline) as a light yellow solid: LC-MS *m/z* 395 (MH⁺), retention time 3.91 min (method 1); mp 143-144°C; R_f = 0.63 (50% EtOAc in hexane). ¹H NMR (300 MHz, CDCl₃) δ 1.39-1.43 (3H, t, J = 7.2 Hz), 4.39-4.46 (2H, q, J = 6.9 Hz), 7.04-7.08 (2H, m), 7.25-7.50 (5H, m), 7.89 (1H, s).

15

Example 5Preparation of ethyl 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazole-4-carboxylate

20

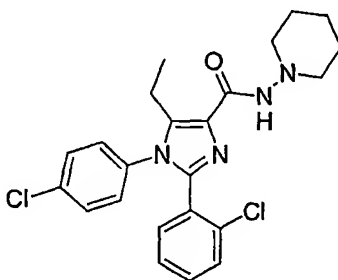
A solution of 2-dichloro-*N*-(4-chlorophenyl)benzenecarboximidamide (10 g, 37.7 mmol) in THF (100 mL) was treated with K₂CO₃ (5.2g, 37.7 mmol) followed by the slow addition of ethyl 3-bromo-2-oxopentanoate (10.1 g, 45 mmol) over 3 h. The reaction mixture was stirred at rt overnight. The solid was then filtered off and the solvent was evaporated. The residue (20 g, 37.7 mmol) was dissolved in acetic acid (100 mL) and heated at reflux for 1 h. The reaction mixture

25

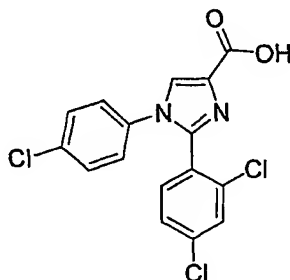
was cooled to rt, diluted with water (200 mL), and extracted with ethyl acetate. The organic layer was washed with water. The aqueous layer was neutralized with saturated NaHCO₃, and extracted with ethyl acetate. The combined extracts were dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography over silica gel (40% ethyl acetate in hexane) to give the product (8.5 g, 40% overall yield from 4-chloroaniline) as a light yellow solid: LC-MS *m/z* 389 (MH⁺), retention time 3.31 min (method 1); R_f = 0.28 (40% EtOAc in hexane). ¹H NMR (300 MHz, CDCl₃) δ 1.05-1.10 (3H, t, J = 7.5 Hz), 1.40-1.44 (3H, t, J = 7.2 Hz), 2.85-2.92 (2H, q, J = 4.2 Hz), 4.39-4.46 (2H, q, J = 7.2 Hz), 7.09-7.41 (8H, m).

Example 6

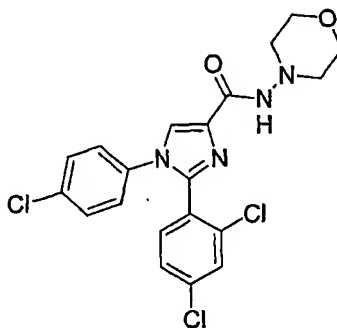
Preparation of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide



To a solution of 1-aminopiperidine (2.48 mL, 23 mmol) in CH₂Cl₂ (15 mL) was added trimethylaluminum (11.5 mL, 2 M in hexane, 23 mmol). After the mixture was stirred for 0.5 h, a solution of ethyl 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazole-4-carboxylate (3.0 g, 7.7 mmol) in CH₂Cl₂ (10 mL) was added. The reaction mixture was heated at reflux for 2 h and cooled to rt. Water was slowly added dropwise to the reaction mixture at 0°C until no more gas bubbled out. The mixture was dried over Mg₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography over silica gel (40 % then 60% ethyl acetate in hexane) to give the product (2.4 g, 64 % yield) as a white solid: LC-MS *m/z* 443 (MH⁺), retention time 2.95 min (method 1); mp 208-209 °C; R_f = 0.74 (EtOAc). ¹H NMR (300 MHz, CDCl₃) δ 0.98-1.03 (3H, t, 7.8 Hz), 1.35-1.37 (2H, m), 1.58-1.70 (4H, m), 2.77-2.88 (6H, m), 6.70-7.30 (8H, m), 7.84 (1H, s).

Example 7Preparation of 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-5H-imidazole-4-carboxylic acid

To a solution of ethyl 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-
 5 carboxylate (1.1 g, 2.79 mmol) in MeOH (20 mL), a solution of KOH (2.2 g, 39 mmol) in H₂O (20 mL) was added. The mixture was heated at 90°C for 3 h. The reaction mixture was cooled to rt and the MeOH was evaporated. HCl (1N) was added until a white precipitate formed. The solid was filtered off, and dried under vacuum. The product (1.0 g, 98% yield) was obtained as a white solid: LC-MS *m/z* 367 (MH⁺), retention time is 3.43 min (method 1); mp 150-151 °C; ¹H NMR
 10 (300 MHz, CDCl₃) δ 7.24-7.65 (7H, m), 8.26 (1H, s).

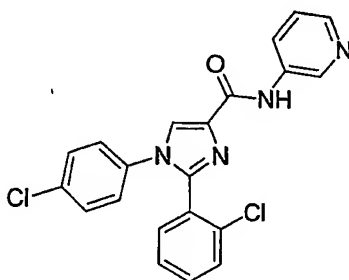
Example 8Preparation of 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide

To a solution of 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-5H-imidazole-4-carboxylic acid (50 mg, 0.137 mmol) in CH₂Cl₂ (5 mL), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (58 mg, 0.164 mmol), 1-hydroxy-7-azabenzotriazole (40 mg, 0.164 mmol), and triethylamine (1.5 mL) were added. After the mixture was stirred for 15 minutes, 4-morpholinamine (0.164 mmol) was added. The reaction mixture was stirred at rt overnight, and

washed with water. The organic layer was dried over MgSO_4 , filtered, and concentrated. The residue was purified by HPLC (YMC-packed PRO C18 15 x 200 mm column, 10-90% CH_3CN in $\text{H}_2\text{O}/\text{TFA}$, 20 mL/min.) to give the product (10 mg, 16% yield) as a yellow oil: LC-MS m/z 451 (MH^+), retention time 3.03 min (method 1); R_f = 0.57 (50% EtOAc in hexane); ^1H NMR (300 MHz, CDCl_3) δ 2.97-3.00 (4H, t, J = 4.5 Hz), 3.83 – 3.86 (4H, t, J = 4.2 Hz), 7.04 – 7.39 (8H, m), 7.92 (1H, s).

Example 9

Preparation of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(3-pyridinyl)-1*H*-imidazole-4-carboxamide



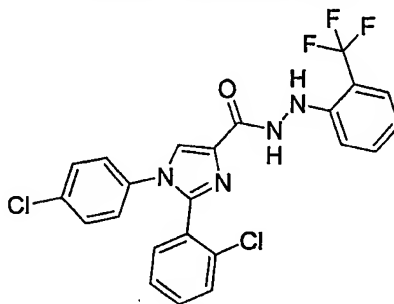
10

2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid (403 mg, 1.2 mmol) was dissolved in dichloromethane (5 mL) and treated with *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (459 mg, 1.56 mmol) and *N*-methylmorpholine (NMM) (182 mg, 1.8 mmol). The mixture was stirred under argon for 15 minutes before 3-aminopyridine (349 mg, 3.6 mmol) was added. Stirring at rt was continued overnight. The reaction mixture was then adsorbed onto silica gel and chromatographed (2-3% MeOH in CH_2Cl_2) to afford 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(3-pyridinyl)-1*H*-imidazole-4-carboxamide (266 mg, 54% yield): LC-MS m/z 409.3, retention time 2.43 min (method 1).

15

Example 10

Preparation of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*'-[2-(trifluoromethyl)phenyl]-1*H*-imidazole-4-carbohydrazide

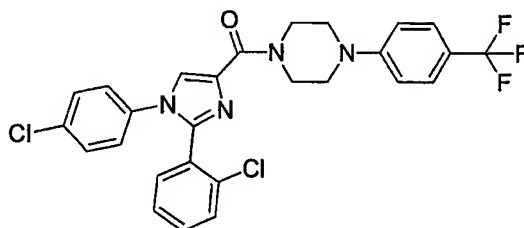


In a 20-mL screw-cap vial, 100 mg (0.3 mmol) 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxylic acid, 87 mg (0.33 mmol) TFFH (Advanced Chemtech, Louisville, KY), and 5.0 equiv. PS-DIEA (Argonaut Technologies Inc., San Carlos, CA) (loading level: 3.50 mmol/g, 429 mg, 1.5 mmol) were heated in 8 mL 1,2-dichloroethane at 35°C overnight. The formation of acyl fluoride was monitored by LC-MS. To the mixture, 1.1 equiv. (58 mg, 0.33 mmol) 2-(trifluoromethyl)phenyl hydrazine was added and the reaction continued overnight. The mixture was filtered through a filter tube (polypropylene frit), and the filtrate was evaporated under reduced pressure. The crude product was redissolved in 1 mL MeOH and purified by preparative HPLC to give 41.8 mg of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide as the trifluoroacetate salt (light yellow solid, 23% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.70 (s, 1 H), 7.85 (s, 1 H), 7.45 (m, 2 H), 7.20-7.38 (m, 6 H), 7.12 (d, 1 H), 7.00 (d, 2 H), 6.88 (t, 1 H), 6.60 (s, 1 H); LC-MS *m/z* 491.2 (MH⁺), retention time 4.02 min (method 2).

The free base form of the product was obtained by dissolving the TFA salt in dichloromethane, washing with saturated aqueous sodium carbonate solution and water, followed by drying the organic phase with magnesium sulfate, and evaporation of the organic phase under reduced pressure. The hydrochloride salt form of the product was obtained by treating the free base in dichloromethane with 1.0 M hydrogen chloride in diethyl ether until no more precipitate was formed, followed by evaporation of solvent under reduced pressure.

Example 11

Preparation of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[4-(trifluoromethyl)phenyl]piperazine

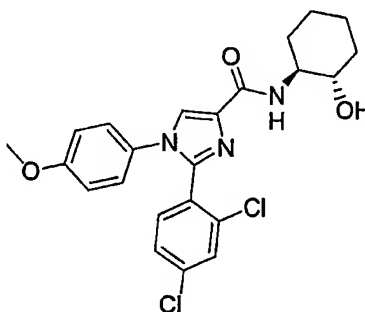


In a 20-mL screw-cap vial, 100 mg (0.3 mmol) 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxylic acid, 87 mg (0.33 mmol) TFFH, and 5.0 equiv. PS-DIEA (loading level: 3.50 mmol/g, 429 mg, 1.5 mmol) were heated in 8 mL 1,2-dichloroethane at 35°C overnight. The formation of acyl fluoride was monitored by LC-MS. To the mixture, 1.1 equiv. (76 mg, 0.33

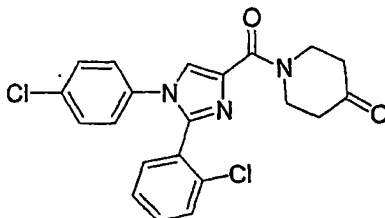
mmol) 1-(4-trifluoromethylphenyl)-piperazine was added and the reaction continued overnight. The mixture was filtered through a filter tube (polypropylene frit), and the filtrate was evaporated under reduced pressure. The crude product was redissolved in 1 mL MeOH and purified by preparative HPLC to give 45.9 mg of 1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-[4-(trifluoromethyl)phenyl]piperazine as the trifluoroacetate salt (yellow oil, 23% yield). ¹H NMR (400 MHz, CD₃COCD₃) δ 7.95 (s, 1 H), 7.60 (m, 1 H), 7.30-7.50 (m, 7 H), 7.25 (d, 2 H), 7.05 (d, 2 H), 4.5 (bs, 2 H), 3.80 (bs, 2 H), 3.35 (m, 4 H); LC-MS *m/z* 545.3 (MH⁺), retention time 4.21 min (method 2).

Example 12

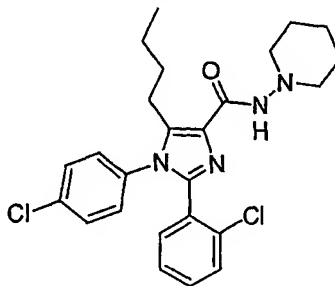
2-(2,4-dichlorophenyl)-N-(trans-2-hydroxycyclohexyl)-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide



In a 20-mL screw-cap vial, 182 mg (0.5 mmol) 2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazole-4-carboxylic acid, 145 mg (0.55 mmol) TFFH, and 5.0 equiv. PS-DIEA (loading level: 3.50 mmol/g, 716 mg, 2.5 mmol) were heated in 10 mL 1,2-dichloroethane at 35°C overnight. The formation of acyl fluoride was monitored by LC-MS. To the mixture, 1.1 equiv. (84 mg, 0.55 mmol) trans-2-aminocyclohexanol hydrochloride was added and the reaction continued overnight. The mixture was filtered through a filter tube (polypropylene frit), and the filtrate was evaporated under reduced pressure. The crude product was redissolved in 1 mL MeOH and purified by preparative HPLC to give 53 mg of 2-(2,4-dichlorophenyl)-N-(trans-2-hydroxycyclohexyl)-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide (amber oil, 23% yield). ¹H NMR (400 MHz, CD₂Cl₂) δ 7.90 (s, 1 H), 7.30-7.50 (m, 4 H), 7.10 (d, 2 H), 6.90 (d, 2 H), 3.85 (s, 3 H), 3.80 (m, 1 H), 3.50 (m, 1 H), 3.25 (bs, 1 H), 2.0 (m, 2 H), 1.75 (m, 2 H), 1.30-1.50 (m, 4 H); LC-MS *m/z* 460.2 (MH⁺), retention time 3.31 min (method 2).

Example 13Preparation of 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-4-piperidinone

- 5 Step 1. Thionyl chloride (0.66 mL, 9 mmol) was added to a solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxylic acid (1 g, 3 mmol) in toluene (10 mL). The mixture was refluxed under argon for 1.5 h and concentrated to provide 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbonyl chloride, which was used in the next step without purification. ¹H NMR (300 MHz, CD₂Cl₂) δ 8.40 (s, 1H), 7.69-7.09 (m, 8H).
- 10 Step 2. Triethylamine (1.46 mL, 10.45 mmol) was added to a suspension of 4-piperidinone trifluoroacetate (0.76 g, 3.58 mmol) in CH₂Cl₂ (10 mL) and a solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbonyl chloride in CH₂Cl₂ (5 mL) was added. The mixture was stirred at rt under argon for 17 h, diluted with CH₂Cl₂ (50 mL), washed with water (2 × 50 mL), dried over MgSO₄, and concentrated to give 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-4-piperidinone as a yellow solid (0.96 g, 77 %). MS (Electrospray) 414 (MH⁺), ¹H NMR (300 MHz, CD₂Cl₂) δ 7.80 (s, 1H), 7.37-7.20 (m, 6H), 7.06-7.00 (m, 6H), 4.47 (br, 2H), 3.92 (br, 2H), 2.46 (t, 4H).
- 15

Example 1420 5-Butyl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide

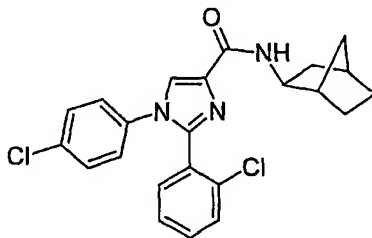
- 25 Step 1. To a solution of 5-butyl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxylic acid (438 mg, 1.12 mmol) in dry toluene (3 mL), at rt was added thionyl chloride (401 μL, 3.4 mmol). The solution was stirred overnight at rt, and then heated at 110°C for 5 h.

The resulting reaction was cooled to rt, and the solvents evaporated, to give 5-butyl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carbonyl chloride (455 mg, 100%), which was used in the next step without purification. LC-MS *m/z* 407 (MH^+), retention time 3.62 min (method 2).

Step 2. To a solution of 5-butyl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carbonyl chloride (227 mg, 0.56 mmol) in CH_2Cl_2 (5 mL), were added 1-aminopiperidine (113 mg, 1.12 mmol) and Et_3N (234 μ L, 1.68 mmol). The solution was stirred overnight at rt, and then the solvents were evaporated under reduced pressure. The residue was purified by preparative reversed-phase HPLC, using 20 to 100% MeCN in water as gradient, to provide 125 mg (48 %) of 5-butyl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide as a white powder. 1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.27 (m, 8 H), 2.93 (t, 2 H), 2.82 (bs, 4 H), 1.77-1.71 (m, 4 H), 1.46-1.37 (m, 4 H), 1.25-1.20 (2 H), 0.79 (t, 3 H). LC-MS *m/z* 471.33 (MH^+), retention time 2.88 min (method 2).

Example 15

Preparation of *N*-exo-bicyclo[2.2.1]hept-2-yl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxamide



Step 1. 2-(2-Chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid (1.5 g, 4.5 mmol) was dissolved in dichloromethane (40 mL). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 946 mg, 4.95 mmol) and triethylamine (500 mg, 4.95 mmol) were added followed by pentafluorophenol (815 mg, 4.37 mmol). The mixture was stirred at rt under argon for one hour before it was washed with 5% HCl, sodium bicarbonate solution, and then brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give the crude product (1.26 g) which was chromatographed over silica gel (20% EtOAc in hexanes) to afford pentafluorophenyl 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylate (0.73 g, 32% yield); LC-MS *m/z* 499.0 (MH^+), retention time 3.93 min (method 1).

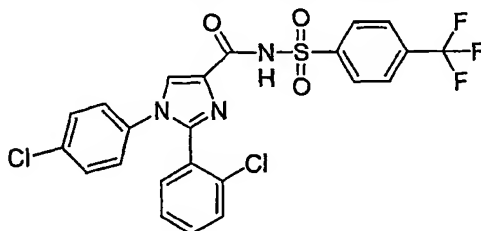
Step 2. The pentafluorophenol ester (60 mg, 0.12 mmol) and exo-norbornylamine (40 mg, 0.36 mmol) were dissolved in dichloromethane (2 mL), treated with triethylamine (49 mg, 0.48 mmol), and stirred at rt overnight. The mixture was then washed with 5% aqueous HCl, sodium

bicarbonate solution and brine, dried (MgSO₄), filtered, and concentrated. Pure *N*-exo-bicyclo[2.2.1]hept-2-yl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxamide was thus obtained (30 mg, 59% yield): LC-MS *m/z* 426.1 (MH⁺), retention time 3.49 min (method 1).

5

Example 16

Preparation of *N*-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-(trifluoromethyl) benzenesulfonamide

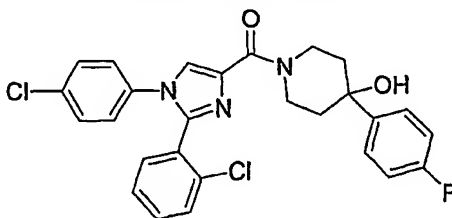


In a 20-mL screw-cap vial, 250 mg (0.75 mmol) 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid, 18.3 mg DMAP (0.15 mmol), 1.25 g PS-Carbodiimide (1.5 mmol) (polystyrene-supported cyclohexylcarbodiimide, Argonaut Technologies Inc., San Carlos, CA), 169 mg α,α,α -trifluoro-*p*-toluenesulfonamide (0.75 mmol), and 12 mL dichloromethane were added, and the reaction mixture was mixed by orbital shaking at rt overnight. The reaction mixture was filtered through a filter tube (polypropylene frit), and the filtrate was evaporated under reduced pressure. The crude product was redissolved in 2 mL MeOH and purified by preparative HPLC to give 39.3 mg of *N*-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-(trifluoromethyl)benzenesulfonamide (beige solid, 10% yield). ¹H NMR (400 MHz, CD₃COCD₃) δ 8.25 (d, 2 H), 7.85 (s, 1 H), 7.75 (s, 2H), 7.20-7.40 (m, 6 H), 6.95 (t, 2 H); LC-MS *m/z* 540 (MH⁺), retention time 3.36 min (method 2).

20

Example 17

Preparation of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-(4-fluorophenyl)-4-piperidinol



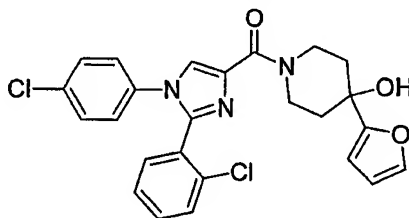
25

A solution of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-(4-fluorophenyl)-4-piperidinone (0.1 g, 0.24 mmol, prepared as described in Example 13) in THF (4 mL) was added

dropwise to a solution of 4-fluorophenylmagnesium bromide (0.6 mL, 0.60 mL) at -78°C . The mixture was stirred at -78°C for 2 h then allowed to warm up to 30°C . Saturated NH_4Cl (3 mL) was added slowly followed by water (3 mL). The mixture was extracted with ethyl acetate (3 x 20 mL) and dried over MgSO_4 . The product (0.056 g, 46 %) was isolated by column (50 % ethyl acetate in hexane). MS (Electrospray) 510.1 (M^+); ^1H NMR (300 MHz, CD_2Cl_2) δ 7.81 (s, 1H), 7.50-7.24 (m, 8H), 7.10-6.98 (m, 4H), 5.33-5.17 (m, 1H), 4.74-4.57 (m, 1H), 3.68 (t, 1H), 3.31 (t, 1H), 2.15 (br, 2H), 1.83 (d, 2H).

Example 18

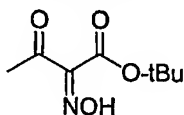
Preparation of 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-4-(2-furyl)-4-piperidinol



BuLi (0.875 mL, 1.40 mmol, 1 M solution in THF) was added slowly to a solution of furan (0.106 mL, 1.45 mmol) in THF (2 mL) at -78°C , and the mixture was stirred at -78°C for 1 h. A solution of 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-4-piperidinone (0.3 g, 0.68 mmol) in THF (1 mL) was added slowly. The mixture was stirred at -78°C for 2 h and saturated NH_4Cl (3 mL) and water added. The mixture was extracted with ethyl acetate (3 x 20 mL) and dried over MgSO_4 . The product (0.142 g, 61 %) was isolated by column (ethyl acetate). MS (Electrospray) 482 (M^+); ^1H NMR (300 MHz, CD_2Cl_2) δ 7.85 (s, 1H), 7.51-7.31 (m, 7H), 7.10-6.98 (m, 4H), 7.17-7.10 (m, 2H), 6.39 (s, 1H), 6.29 (s, 1H), 4.68 (br, 1H), 4.28 (br, 1H), 3.94 (br, 1H), 3.57 (br, 1H), 2.26-1.91 (m, 4H).

Example 19

Preparation of *t*-butyl 2-hydroxyimino-3-oxobutanoate



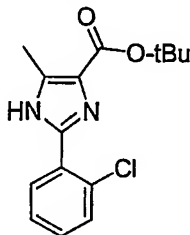
t-Butyl acetoacetate (5.0 g, 31.6 mmol) was dissolved in acetic acid (4.5 mL), cooled by an ice water bath, and treated with sodium nitrite (2.45 g, 35.5 mmol) in water (5.5 mL) while the internal temperature was kept at $<10^{\circ}\text{C}$ (see, e.g., U.S. Patent No. 4,743,586). After the addition

was complete, the mixture was stirred at rt for 30 minutes before water (16 mL) was added. After 2 h, extraction with ether (3 x 25 mL), which was washed with water (10 mL), sodium bicarbonate solution (3 x 10 mL), and water (20 mL), gave *t*-butyl 2-hydroxyimino-3-oxobutanoate as a white solid (5.52 g, 93%): ¹H NMR (300 MHz, CDCl₃) δ 8.61 (s, 1H), 2.39 (s, 3H), 1.58 (s, 9H).

5

Example 20

Preparation of *t*-Butyl 2-(2-chlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate

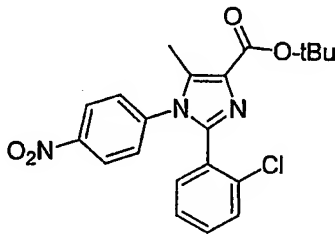


10 *t*-Butyl 2-hydroxyimino-3-oxobutanoate (0.50 g, 2.67 mmol) was mixed with 2-chlorobenzylamine (0.34 mL, 2.82 mmol) in anhydrous acetonitrile (10 mL), and heated at reflux for 3 h. Upon cooling, the suspension was filtered, and the filtered material was washed with a small amount of acetonitrile to afford a white solid (0.379 g). The filtrate was concentrated and the residue chromatographed over silica gel (25% EtOAc in hexane) to give *t*-butyl 2-(2-chlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate as a yellow foam (0.262 g, 82% combined yield): ¹H NMR (300 MHz, CDCl₃) δ 10.43 (br, 1H), 8.29 (m, 1H), 7.38 (m, 3H), 2.52 (s, 3H), 1.60 (s, 9H).

15

Example 21

Preparation of *t*-Butyl 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxylate



20

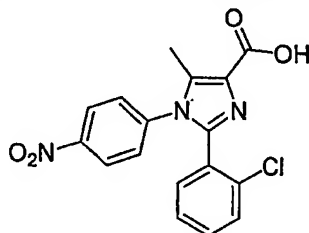
t-Butyl 2-(2-chlorophenyl)-5-methylimidazole-4-carboxylate (70 mg, 0.24 mmol) was mixed with 4-fluoro-1-nitrobenzene (27 μL, 0.25 mmol) and potassium carbonate (66 mg, 0.48 mmol) in dry DMF and heated at 120°C for 4 h. The mixture was diluted with water and filtered to give a yellow solid which was chromatographed over silica gel (40% EtOAc in hexane) to afford a

25

yellow solid (72 mg, 73%): ^1H NMR (300 MHz, CDCl_3) δ 8.20 (m, 2H), 7.51 (m, 1H), 7.25 (m, 5H), 2.45 (s, 3H), 1.66 (s, 9H).

Example 22

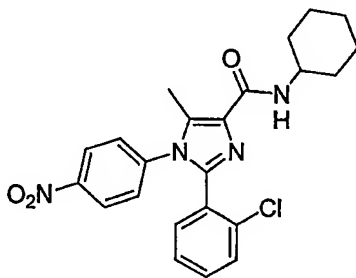
5 Preparation of 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxylic acid



t-Butyl 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxylate (69 mg, 0.17 mmol) was dissolved in dry dichloromethane (2 mL) and treated dropwise with trifluoroacetic acid (2 mL). After stirring at rt for 2 h, the solution was concentrated to give 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxylic acid as a yellow foam, which was used without purification in the preparation of Example 23.

Example 23

15 Preparation of *N*-cyclohexyl-2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxamide



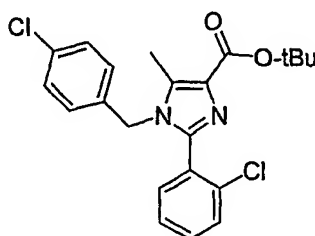
The carboxylic acid obtained from Example 22 was dissolved in dry dichloromethane (3 mL), cooled by an ice water bath, and treated with 1-(3-dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (39 mg, 0.20 mmol) and dimethylaminopyridine (46 mg, 0.38 mmol). The mixture was stirred at rt for 1 h before cyclohexylamine (23 μL , 0.20 mmol) was added. The solution was stirred overnight, diluted with dichloromethane, washed with water and ammonium chloride solution, dried (sodium sulfate), and filtered. The filtrate was concentrated to afford a yellow oil (70 mg) which was chromatographed over silica gel (35% EtOAc in hexane) to

give *N*-cyclohexyl-2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-imidazole-4-carboxamide as a yellow solid (50 mg, 67%): mp 217-220°C; ¹H NMR (300 MHz, CDCl₃) δ 8.20 (d, 2H), 7.41 (m, 1H), 7.25 (m, 5H), 7.12 (m, 1H), 3.95 (m, 1H), 2.55 (s, 3H), 2.00 (m, 2H), 1.75 (m, 2H), 1.61 (m, 1H), 1.30 (m, 5H); LC-MS *m/z* 439.2 (MH⁺), retention time 3.41 min (method 1).

5

Example 24

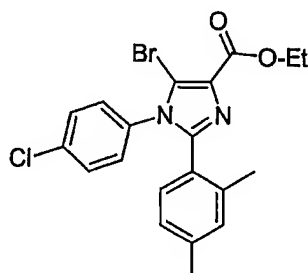
Preparation of tert-butyl 1-(4-chlorobenzyl)-2-(2-chlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate



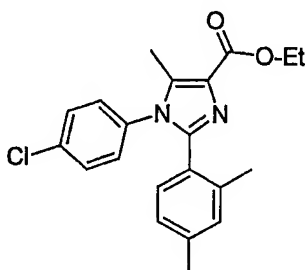
10

t-Butyl 2-(2-chlorophenyl)-5-methylimidazole-4-carboxylate (70 mg, 0.24 mmol) was mixed with 4-chlorobenzyl bromide (50 mg, 0.24 mmol) and potassium carbonate (66 mg, 0.48 mmol) in dry acetonitrile (3 mL) and heated at reflux overnight. The next day, additional 4-chlorobenzyl bromide (10 mg, 0.05 mmol) was added, and the reaction mixture was again heated at reflux overnight. The next day, water was added to the cooled mixture, which was subsequently extracted with EtOAc. The extract was washed with aqueous NaCl, dried (NaSO₄), filtered, and concentrated to give a colorless oil (113 mg). It was chromatographed over silica gel (25% EtOAc in hexane) to afford tert-butyl 1-(4-chlorobenzyl)-2-(2-chlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate as a white foam (61 mg, 61% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.48 (d, 1H), 7.40 (m, 1H), 7.27 (m, 2H), 7.17 (d, 2H), 6.78 (d, 2H), 5.33 (br, 2H), 2.55 (s, 3H), 1.50 (s, 9H); LC-MS *m/z* 417.1 (MH⁺), retention time 3.23 min (method 1).

20

Example 25Preparation of ethyl 5-bromo-1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-1H-imidazole-4-carboxylate

Ethyl 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-1H-imidazole-4-carboxylate (1.23 g, 3.47 mmol) was dissolved in EtOH (15 mL) and treated with *N*-bromosuccinimide (1.25 g, 7.02 mmol). The solution was stirred at rt for 3 h. Water was added. Extraction with dichloromethane, which was then washed with NaCl solution, gave an orange solid (1.94 g). Purification by chromatography over silica gel (20% EtOAc in hexane) afforded a light tan solid (1.028 g, 68%): ¹H NMR (300 MHz, CDCl₃) δ 7.35 (d, 2H), 7.03 (d, 2H), 7.00 (m, 1H), 6.86 (m, 2H), 4.44 (q, 2H), 2.26 (s, 3H), 2.10 (s, 3H), 1.43 (t, 3H); LC-MS *m/z* 433.1 (MH⁺), retention time 3.84 min (method 1).

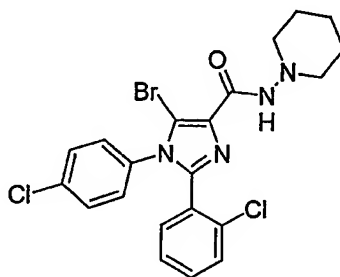
Example 26Preparation of ethyl 1-(4-chlorophenyl)-5-methyl-2-(2,4-dimethylphenyl)-1H-imidazole-4-carboxylate

Ethyl 5-bromo-1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-1H-imidazole-4-carboxylate (430 mg, 0.99 mmol) was dissolved in dry DMF (5 mL) in a pressure tube and treated with tetramethyltin (1.3 mL, 9.38 mmol), palladium acetate (9 mg, 0.04 mmol), and tri-(*o*-tolyl)phosphine (26 mg, 0.085 mmol). The mixture was heated at 110°C for 15 minutes. After the

mixture was cooled to rt, water was added (25 mL). The mixture was extracted with dichloromethane (2 x 25 mL), and the organic phase was washed with water, dried (Na₂SO₄), filtered, and concentrated, to give a light brown oil (436 mg). Purification by chromatography over silica gel (33% EtOAc in hexane) afforded ethyl 1-(4-chlorophenyl)-5-methyl-2-(2,4-dimethylphenyl)-1*H*-imidazole-4-carboxylate as a white foam (338 mg, 93% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.30 (d, 2H), 7.00 (m, 3H), 6.85 (m, 2H), 4.41 (q, 2H), 2.42 (s, 3H), 2.23 (s, 3H), 2.06 (s, 3H), 1.41 (t, 3H).

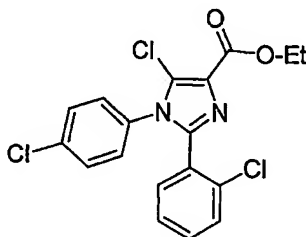
Example 27

Preparation of 5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(1-piperidiny)-1*H*-imidazole-4-carboxamide



Step 1. A solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid (50 mg, 0.15 mmol) and *N*-bromosuccinimide (88 mg, 0.49 mmol) in dimethylformamide (5 mL) was stirred at 75°C for 3 days. The solution was purified by preparative HPLC to give 5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid as a white solid (30.7 mg, 50%). LC-MS *m/z* 411.2 (MH⁺), retention time 2.70 min (method 2).

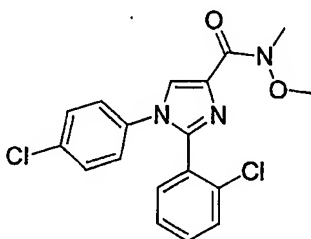
Step 2. As described previously for Example 14, 5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylic acid was converted to 5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(1-piperidiny)-1*H*-imidazole-4-carboxamide. LC-MS *m/z* 493.0 (MH⁺), retention time 2.63 min (method 2). ¹H NMR (CD₂Cl₂, 400 MHz) δ 7.29 (m, 6H, Ph), 7.05 (m, 2H, Ph), 3.68 (m, 3H, piperidine), 3.36 (m, 2H, piperidine), 1.88 (m, 3H, piperidine), 1.57 (m, 2H, piperidine).

Example 28Ethyl 5-chloro-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxylate

5

To a solution of ethyl 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxylate (270 mg, 0.75 mmol) in CH₂Cl₂ (5 mL) was added SO₂Cl₂ (1.6 mL, 20 mmol). The mixture was heated at reflux overnight, and diluted with water. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography over silica gel (33% EtOAc in hexane) to give ethyl 5-chloro-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxylate (60 mg) in 20% yield as a white solid: LC-MS *m/z* 395.0 (MH⁺), retention time 3.45 min (method 1). This intermediate, which is an example of Formula X in Scheme 2, was converted into 5-chloro-2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1-piperidiny)-1H-imidazole-4-carboxamide (Table entry 21).

15

Example 29Preparation of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-methoxy-N-methyl-1H-imidazole-4-carboxamide

20

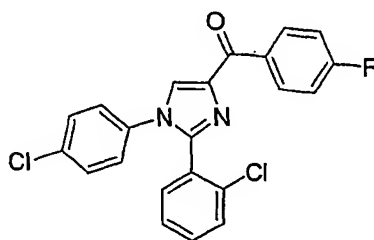
A solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbonyl chloride (4.71 g, 13.4 mmol, prepared by the method described in Example 13, step 1) in 10 mL dichloromethane was added to a solution of *N*, *O*-dimethylhydroxyamine hydrochloride (1.44 g, 14.7 mmol) and triethylamine (5.6 mL, 40.2 mmol) in 60 mL dichloromethane in an ice water bath under argon with stirring. The bath was removed upon completion of addition. Stirring was

25

continued for 1 h. Water was added and the mixture was extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and concentrated down under reduced pressure. The crude product was purified on silica gel, eluting with ethyl acetate to yield 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-methoxy-N-methyl-1H-imidazole-4-carboxamide as an off-white solid (4.20 g, 83%); R_f = 0.22 (ethyl acetate).

Example 30

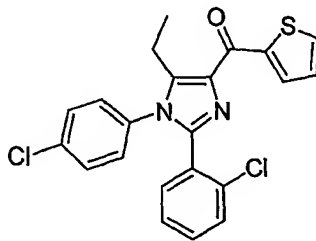
Preparation of [2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](4-fluorophenyl)-methanone



To a solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-methoxy-N-methyl-1H-imidazole-4-carboxamide (50.0 mg, 0.133 mmol) in 1.5 mL THF was added a 1.0 M solution of 4-fluorophenylmagnesium bromide (0.27 mL, 0.27 mmol) under argon at rt with stirring. The resultant mixture was stirred for 30 minutes and a saturated aqueous solution of NH₄Cl was added. The mixture was extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and concentrated down *in vacuo*. The crude product was purified on HPLC to give [2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](4-fluorophenyl)-methanone as a solid (38.0 mg, 69%); R_f = 0.58 (1:1 ethyl acetate / hexanes).

Example 31

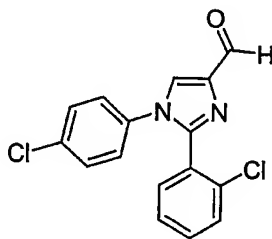
Preparation of [2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl](2-thienyl)-methanone



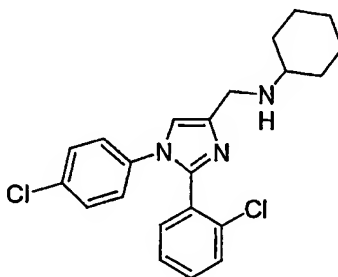
To a solution of 2-bromothiophene (0.22 g, 1.36 mmol) in 2 mL THF was added 0.84 mL of a 1.6 M solution of BuLi in hexane under argon at -78°C with stirring. The stirring was continued for 1 h. To this was added a solution of 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1*H*-imidazol-4-yl]carbonyl}-4-piperidinone in 2 mL THF. The resultant mixture was stirred and gradually allowed to warm up to rt overnight. The reaction was quenched with saturated aqueous NH_4Cl and the mixture was extracted with ethyl acetate. The organic layer was concentrated and the crude product was purified by HPLC to yield [2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1*H*-imidazol-4-yl](2-thienyl)-methanone as a solid (60 mg, 31%); $R_f = 0.13$ (1:5 ethyl acetate / hexanes).

Example 32

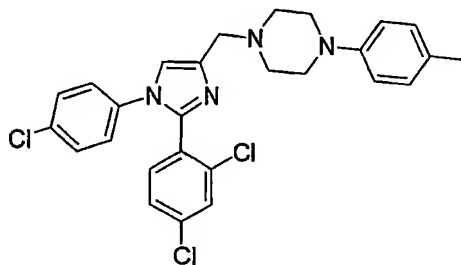
Preparation of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxaldehyde



To a solution of ethyl 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylate (200 mg, 0.51 mmol) in toluene (10 mL) at -78°C was added DIBAH (2.0 mL) in toluene dropwise. The resulting solution was stirred at rt, quenched with 1N HCl (0.5 mL). The organic layer was washed with 1N HCl (5 mL), dried over MgSO_4 , filtered, and concentrated. The residue was purified by flash chromatography (50% EtOAc in hexane) to give the product (62 mg, 38% yield). LC-MS m/z 317.0 (MH^+), retention time: 2.75 min (method 1).

Example 33Preparation of *N*-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]methyl}-*N*-cyclohexylamine

To a solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxaldehyde (62 mg, 0.20 mmol) in methanol (7 mL) was added cyclohexylamine (58 μ L, 0.5 mmol). The mixture was stirred overnight, and cooled to 4°C. NaBH₄ (40 mg, 1.1 mmol) was added. The mixture was stirred at rt for 1 h, and concentrated. The residue was dissolved in CH₂Cl₂, washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by preparative TLC (50% EtOAc in hexane) to give *N*-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]methyl}-*N*-cyclohexylamine (65 mg, 81% yield): LC-MS *m/z* (400.7 MH⁺), retention time 2.32 min (method 1).

Example 34Preparation of 1-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazol-4-yl]methyl}-4-(4-methylphenyl)piperazine

To a suspension of lithium aluminum hydride (21 mg, 0.54 mmol) in THF (2 mL), 1-(4-methylphenyl)piperazine hydrochloride (32 mg, 0.13 mmol) was added. After 10 minutes, a solution of ethyl 2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxylate (39 mg,

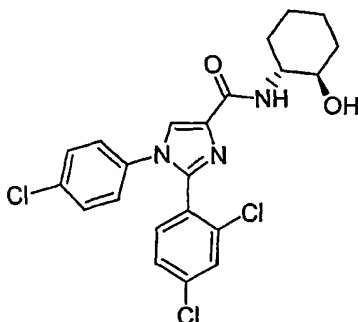
0.1 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 10 minutes, and diluted by water. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by HPLC (YMC-packed Pro C18 20 x 150 mm column, 10-90% CH₃CN in H₂O/TFA, 25 mL/min) to give the product 1- $\{[1-(4\text{-chlorophenyl})-2-(2,4\text{-dichlorophenyl})-1H\text{-imidazol-4-yl]methyl}\}$ -4-(4-methylphenyl)-piperazine (1.4 mg, 2% yield): LC-MS m/z 511.1 (MH⁺), retention time 2.94 min (method 1). ¹H NMR (300 MHz, CDCl₃) δ : 2.29 (3H, s), 3.42-3.49 (8H, br), 4.39 (2H, s), 6.85-7.41 (11H, m), 7.54 (1H, s).

Other Procedures

In certain cases, the products and intermediates prepared by the experimental methods described in Examples 1-34 were converted into additional products, by applying the appropriate additional chemical steps. These additional examples are described below.

Example 35

1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-[(1*R*,2*R*)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide

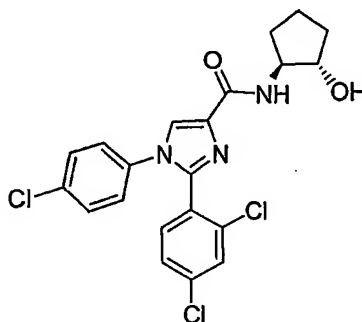


To a solution of *N*-[(1*R*, 2*R*)-2-(benzyloxy)cyclohexyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxamide (Table entry 278, prepared according to the procedures described in Examples 13 and 14) (100 mg, 0.18 mmol) in CH₂Cl₂ (2 mL), TMSI (iodotrimethylsilane) (60 μ L, 0.42 mmol) was added. The mixture was stirred at rt overnight, and diluted with water. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc) to afford 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-[(1*R*,2*R*)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide (56 mg, 67% yield) as a yellow solid: LC-MS m/z 464.3 (MH⁺), retention time 3.19 min (method 1); R_f = 0.67

(EtOAc); ^1H NMR (300 MHz, CDCl_3) δ 1.16-1.30 (4H, m), 1.66-1.69 (2H, m), 1.98-2.02 (2H, m), 3.37-3.39 (1H, m), 3.70-3.80 (1H, m), 3.99-4.06 (1H, m), 6.96- 7.37 (8H, m), 7.78 (1H, s).

Example 36

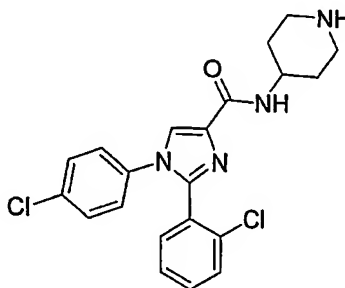
5 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1S, 2S)-2-hydroxycyclopentyl]-1H-imidazole-4-
carboxamide



To a solution of *N*-[(1S, 2S)-2-(benzyloxy)cyclopentyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxamide (Table entry 282, prepared according to the procedures described in Examples 13 and 14) (119 mg, 0.22 mmol) in CH_2Cl_2 (4 mL), TMSI (0.2 mL, 1.4 mmol) was added. The mixture was stirred at rt overnight, and diluted by water. The organic layer was dried over MgSO_4 , filtered, and concentrated. The residue was purified by preparative TLC (EtOAc) to afford 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-[(1S, 2S)-2-hydroxycyclopentyl]-1*H*-imidazole-4-carboxamide (80 mg, 82% yield) as a white foam: LC-MS m/z 450.0 (MH^+), retention time 3.24 min (method 1); R_f = 0.45 (50% EtOAc in hexane); ^1H NMR (300 MHz, CDCl_3) δ 1.22-2.24 (6H, m), 3.97-4.15 (2H, m), 7.03-7.42 (7H, m), 7.86 (1H, s).

Example 37

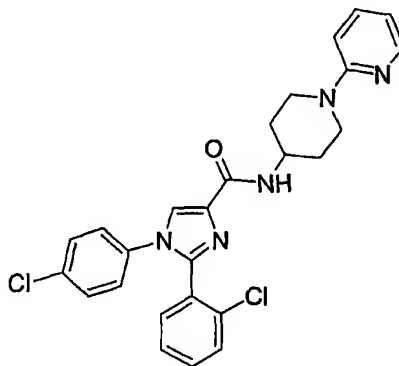
20 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-piperidiny)-1H-imidazole-4-carboxamide



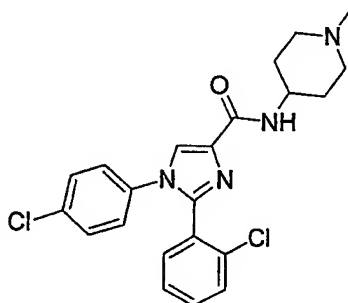
To a solution of ethyl 4-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl)amino)-1-piperidinecarboxylate (Table entry 221) (0.595 g, 1.221 mmol) in CH₂Cl₂ (10 mL) was added TMSI (0.176 mL, 2.7 mmol). The mixture was heated at reflux for 3 h, diluted by methanol, and concentrated. The residue was dissolved in methanol and NaOMe (0.62 mmol) was added. The mixture was concentrated and purified by flash chromatography (2M NH₃ in methanol : EtOAc = 15: 85) to afford the product 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(4-piperidinyl)-1*H*-imidazole-4-carboxamide (180 mg, 36% yield): LC-MS *m/z* 415.3 (MH⁺), retention time 2.22 min (method 1); R_f = 0.25 (1:1 EtOAc/2M NH₃ in MeOH). ¹H NMR (300 MHz, CDCl₃) δ 1.35-1.51 (2H, m), 1.91-2.15 (3H, br), 2.63-2.78 (2H, m), 3.03-3.09 (2H, m), 3.97-4.15 (1H, m), 6.96-7.52 (8H, m), 7.81 (1H, s).

Example 38

2-(2-Chlorophenyl)-1-(4-chlorophenyl)-*N*-[1-(2-pyridinyl)-4-piperidinyl]-1*H*-imidazole-4-carboxamide



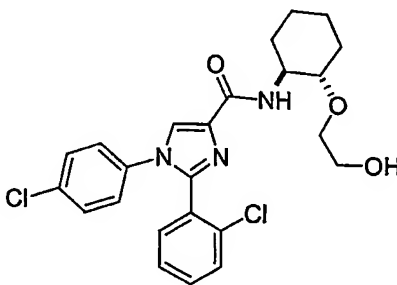
A flask was charged with 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-(4-piperidinyl)-1*H*-imidazole-4-carboxamide (Example 37) (100 mg, 0.24 mmol), 2-bromopyridine (0.55 mg, 0.22 mmol), Pd₂(dba)₃ (38 mg, 0.24 mmol), BINAP (1.18 mg, 0.0019 mmol), NaO*t*Bu (33.6 mg, 0.35 mmol), and toluene (2 mL). The reaction mixture was heated at reflux overnight, cooled to rt, and diluted with CH₂Cl₂. The solid was filtered off. The solvent was evaporated. The residue was purified by flash chromatography (33% EtOAc in hexane) to give the product 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[1-(2-pyridinyl)-4-piperidinyl]-1*H*-imidazole-4-carboxamide (55 mg, 47% yield): LC-MS *m/z* 492.1 (MH⁺), retention time 2.47 min (method 1); R_f = 0.33 (50% EtOAc in hexane).

Example 392-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1-methyl-4-piperidiny)-1H-imidazole-4-carboxamide

5

To a solution of 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-piperidiny)-1H-imidazole-4-carboxamide (Example 37) (80 mg, 0.2 mmol) in CH_2Cl_2 (6 mL) was added CH_3I (28.4 mg, 0.2 mmol) and Et_3N (0.031 mL, 0.22 mmol). The reaction mixture was heated at reflux for 5 h, cooled to rt, and washed with brine. The organic layer was dried over MgSO_4 , filtered, and concentrated. The residue was purified by flash chromatography (2M NH_3 in methanol : EtOAc = 1:10) to afford the product 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1-methyl-4-piperidiny)-1H-imidazole-4-carboxamide (24 mg, 28% yield): LC-MS m/z 429.1 (MH^+), retention time 2.27 min (method 1); R_f = 0.31 (EtOAc: 2M NH_3 in MeOH = 9:1).

15

Example 402-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[trans-2-(2-hydroxyethoxy)cyclohexyl]-1H-imidazole-4-carboxamide

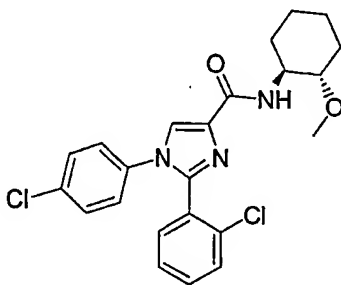
20

To a solution of 2-[[trans-2-({[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}amino)cyclohexyl]oxy}-ethyl acetate (Table entry 286) (31 mg, 0.06 mmol) in THF (7 mL) and water (0.7 mL) was added NaBH_4 (5 mg, 0.13 mmol) portionwise over 1 h with the

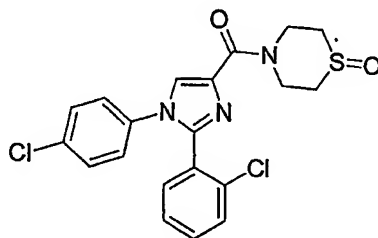
temperature kept below 20°C. The mixture was stirred at rt overnight, cooled to 5°C, treated with acetone (1 mL), and then concentrated. The residue was dissolved in CH₂Cl₂ and washed with brine. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (2.5% methanol in EtOAc) to give the product 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[(1*R*, 2*S*)-2-(2-hydroxyethoxy)cyclohexyl]-1*H*-imidazole-4-carboxamide (7.5 mg, 26% yield): LC-MS *m/z* (474.8 MH⁺), retention time 2.91 min (method 1); R_f = 0.17 (EtOAc).

Example 41

2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[trans-2-methoxycyclohexyl]-1*H*-imidazole-4-carboxamide



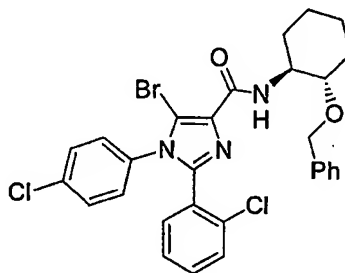
A flask was charged with 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[trans-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide (Table entry 336) (35 mg, 0.1 mmol), benzene (3 mL), 50% aqueous NaOH (2.5 mL), and Bu₄NHSO₄ (17 mg). While the mixture was stirred vigorously at 10°C, CH₃I (19 μL, 0.3 mmol) was added dropwise rapidly. The mixture was stirred for another 30 minutes, and diluted with water (5 mL) and hexane (10 mL). The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (75% EtOAc in hexane) to give the product 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[(1*R*, 2*S*)-2-methoxycyclohexyl]-1*H*-imidazole-4-carboxamide (23 mg, 63% yield): LC-MS *m/z* 444.2 (MH⁺), retention time 3.24 min (method 1).

Example 424-{{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}thiomorpholine 1-oxide

5

To a solution of 4-{{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}thiomorpholine (Table entry 176) (30 mg, 0.072 mmol) in acetone (2 mL), was added 30% aqueous H₂O₂ (0.09 mmol). The resulting solution was stirred at rt for 36 h, diluted with water, neutralized with NaHCO₃, and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (20% MeOH in EtOAc) to give the product 4-{{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}thiomorpholine 1-oxide (17 mg, 54% yield): LC-MS *m/z* 434.5 (MH⁺), retention time 2.55 min (method 1); R_f = 0.47 (17% EtOAc in hexane).

15

Example 43*N*-[(1*S*,2*S*)-2-(benzyloxy)cyclohexyl]-5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxamide

20

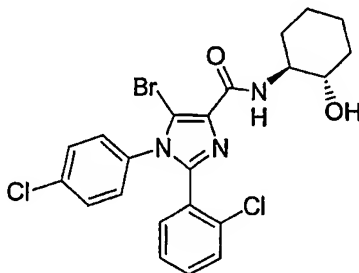
A solution of *N*-[(1*S*,2*S*)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxamide (Table entry 276) (198 mg, 0.380 mmol) and *N*-bromosuccinimide (88 mg, 0.49 mmol) in dimethylformamide (5 mL) was stirred at 75°C for 3 days. The solution was purified by preparative HPLC to give *N*-[(1*S*,2*S*)-2-(benzyloxy)cyclohexyl]-5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-

25

carboxamide as a white solid (196 mg, 86%). LC-MS m/z 598.1 (MH^+), retention time 3.72 min (method 2).

Example 44

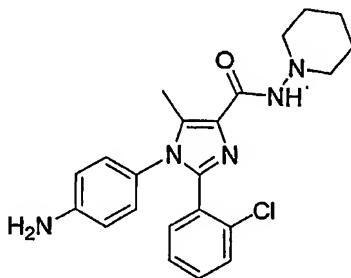
5 5-Bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[(1*S*,2*S*)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide



10 As described previously for Example 35, *N*-[(1*S*,2*S*)-2-(benzyloxy)cyclohexyl]-5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole-4-carboxamide (Example 43) was de-benzylated by treatment with iodotrimethylsilane to give 5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[(1*S*,2*S*)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide. LC-MS m/z 508.1 (MH^+), retention time 2.96 min (method 2). 1H NMR (CD_2Cl_2 , 400 MHz) δ 7.43 (d, 1H, Ph), 7.27 (m, 5H, Ph), 7.06 (m, 2H, Ph), 3.70 (m, 1H, $CHOH$), 3.44 (m, 1H, CHN), 1.95 (m, 2H, cyclohexane), 1.64 (m, 2H, cyclohexane), 1.24 (m, 4H, cyclohexane).

Example 45

1-(4-Aminophenyl)-2-(2-chlorophenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide



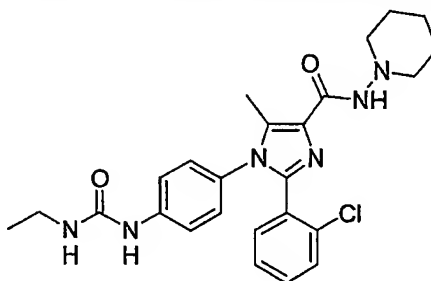
20 A sample of 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide (Table entry 41) (111 mg, 0.25 mmol) was added as a suspension in ethanol (5 mL) to Degussa-type palladium on carbon (10% by weight, 12 mg). The mixture was

hydrogenated at atmospheric pressure and rt for 2 h. Filtration of the mixture through Celite and concentration of the filtrate gave 1-(4-aminophenyl)-2-(2-chlorophenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide as a yellow foam (104 mg, 100%). This material was used without purification for the preparation of compounds of the invention, such as Example 46.

5

Example 46

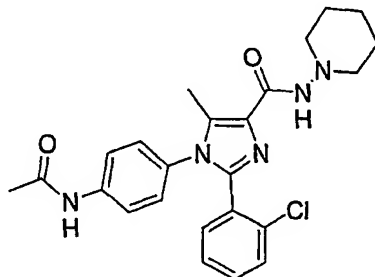
2-(2-chlorophenyl)-1-(4-{{(ethylamino)carbonyl}amino}phenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide trifluoroacetate



10

1-(4-Aminophenyl)-2-(2-chlorophenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide (Example 45) (52 mg, 0.13 mmol) was dissolved in dry dichloromethane (2 mL) and added to ethyl isocyanate (20 μ L, 0.25 mmol). The solution was stirred at rt for 6 h before more ethyl isocyanate (30 μ L, 0.38 mmol) was added. After stirring overnight, the mixture was heated at reflux for 1 h. The solvent was evaporated to give a yellow solid which was chromatographed over silica gel (3% MeOH in EtOAc) to afford semi-pure product (21 mg). This material was further purified by HPLC (YMC-packed Pro C18 15 x 200 mm column, 30-90% CH₃CN in H₂O/TFA, 20 mL/min.) to give 2-(2-chlorophenyl)-1-(4-{{(ethylamino)carbonyl}amino}phenyl)-5-methyl-*N*-(1-piperidinyl)-1*H*-imidazole-4-carboxamide trifluoroacetate as a white solid (12 mg, 13% yield): LC-MS *m/z* 481.4 (MH⁺), retention time 2.35 min (method 1).

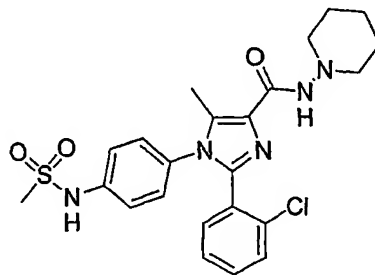
20

Example 471-[4-(acetylamino)phenyl]-2-(2-chlorophenyl)-5-methyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide

5

1-(4-Aminophenyl)-2-(2-chlorophenyl)-5-methyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide (Example 45) (51 mg, 0.12 mmol) was dissolved in dry dichloromethane (2 mL) and treated with acetic anhydride (14 μ L, 0.15 mmol) dropwise. The solution was stirred at rt for 4 h, and then the solvent was evaporated to give an amber oil. It was purified by HPLC (YMC-packed Pro C18 15 x 200 mm column, 30-90% CH_3CN in $\text{H}_2\text{O}/\text{TFA}$, 20 mL/min.) to afford an off-white solid (13 mg, 15%); LC-MS m/z 452.3 (MH^+), retention time 2.31 min (method 1).

10

Example 482-(2-Chlorophenyl)-5-methyl-1-{4-[(methylsulfonyl)amino]phenyl}-N-(1-piperidinyl)-1H-imidazole-4-carboxamide trifluoroacetate

15

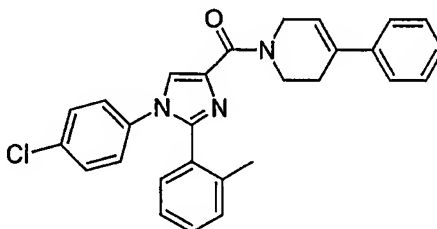
20

1-(4-Aminophenyl)-2-(2-chlorophenyl)-5-methyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide (Example 45) (52 mg, 0.13 mmol) was dissolved in dry dichloromethane (2 mL), cooled by an ice water bath, and the mixture was then treated with methanesulfonyl chloride (12 μ L, 0.16 mmol) and triethylamine (21 μ L, 0.15 mmol). The solution was stirred at rt overnight, and then the solvent was evaporated. The residue was purified by HPLC (YMC-packed Pro C18

15 x 200 mm column, 30-90% CH₃CN in H₂O/TFA, 20 mL/min.) to afford a light tan solid (21 mg, 27%); LC-MS *m/z* 488.4 (MH⁺), retention time 2.29 min (method 1).

Example 49

5 1-{[1-(4-Chlorophenyl)-2-(2-methylphenyl)-1*H*-imidazol-4-yl]carbonyl}-4-phenyl-1,2,3,6-tetrahydropyridine



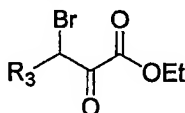
10 A 30-mg sample of 1-{[2-(2-methylphenyl)-1-(4-chlorophenyl)-1*H*-imidazol-4-yl]carbonyl}-4-phenyl-4-piperidinol (Table entry 414), was dissolved in 20 mL dichloromethane, and then 5 mL 2M HCl in ether was added to the solution. Evaporation of the solvent at high temperature (ca. 70°C, 16 hr) in a multiple sample evaporator (GeneVac) gave 1-{[1-(4-chlorophenyl)-2-(2-methylphenyl)-1*H*-imidazol-4-yl]carbonyl}-4-phenyl-1,2,3,6-
15 tetrahydropyridine (yellow solid). ¹H NMR (400 MHz, CD₃COCD₃) δ 8.31 (s, 1H), 7.05-7.35 (m, 13 H), 6.05 (s, 1 H), 4.2 (m, 2 H), 3.85 (m, 2H), 2.5 (m, 2H), 2.0 (s, 3H); LC-MS *m/z* 454 (MH⁺), retention time 2.92 min (method 2).

Preparation of Intermediates

20 Experimental procedures for the preparation of chemical reagents that are not commercially available are described below.

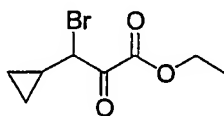
Intermediate A

Ethyl 3-bromo-2-oxobutanoate



25

This bromo pyruvate was prepared by oxidative bromination of the corresponding hydroxyesters, by the procedure described by Plouvier et al., (Heterocycles 32:693-701, 1991). In a similar manner, ethyl 3-bromo-2-oxopentanoate and ethyl 3-bromo-2-oxohexanoate were prepared.

Intermediate BEthyl 3-bromo-3-cyclopropyl-2-oxopropanoate

5

The procedure was similar to that reported in the literature (*see, e.g., J. Org. Chem.* 37, 505-506, 1972).

10 Step 1. To a solution of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (57.5 mL, 0.454 mmol) in CHCl_3 (180 mL) heated at reflux was added dropwise, over a 1-h period, a solution of 1,3-propanedithiol (22.7 mL, 0.227 mmol), followed by ethyl diethoxyacetate (40 g, 0.227 mmol) in CHCl_3 (40 mL). The resulting mixture was heated for 30 minutes, and then cooled to rt. The cooled solution was washed 2 times with water, once with saturated aqueous NaHCO_3 , and then re-washed with water. The combined organic phases were dried over MgSO_4 , then evaporated to give 41 g (94%) of ethyl 1,3-dithiane-2-carboxylate as a yellow oil, which was used in the next step without purification. ^1H NMR (CDCl_3): δ 4.24 (2H, q, $J = 7.2$ Hz), 4.17 (1H, s), 3.46-3.39 (2H, m), 2.64-2.58 (2H, m), 2.18-2.01 (2H, m), 1.30 (3H, t, $J = 7.2$ Hz).

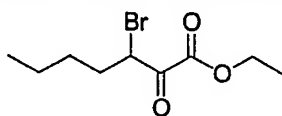
15 Step 2. To a suspension of NaH (95 %, 2.8 g, 111 mmol) in dry toluene (120 mL) stirring at 0°C was dropwise added, over 10 minutes, a solution of bromomethylcyclopropane (15 g, 111 mmol), and ethyl 1,3-dithiane-2-carboxylate (17.77 g, 92.58 mmol) in dry DMF (40 mL). The ice bath was removed and the solution was stirred overnight at rt. Water was added to the solution and the phases were separated. The organic phase was dried over MgSO_4 , then evaporated to give 19.6 g (50%) of ethyl 2-(cyclopropylmethyl)-1,3-dithiane-2-carboxylate, which was used in the next step without purification. ^1H NMR (CDCl_3): δ 4.26 (2H, q, $J = 7.2$ Hz), 3.30-3.23 (2H, m), 2.69-2.64 (2H, m), 2.16-2.11 (1H, m), 1.96 (2H, d, $J = 6.8$ Hz), 1.91-1.81 (1H, m), 1.34 (3H, t, $J = 7.2$ Hz), 0.93-0.86 (1H, m), 0.52-0.47 (2H, m), 0.20-0.16 (2H, m).

20 Step 3. A solution of ethyl 2-(cyclopropylmethyl)-1,3-dithiane-2-carboxylate (19.6 g, 79.67 mmol) in CH_3CN (20 mL) was slowly added, over 30 minutes, to a well-stirred suspension of NBS (N-bromosuccinimide) in CH_3CN (210 mL) and water (55 mL). After the mixture was stirred for 1 h, the resulting red solution was poured into an ice-cold CH_2Cl_2 -Hexane solution (1:1 500 mL). The resulting mixture was washed with saturated aqueous NaHSO_3 and water. The colorless organic phase was carefully washed with saturated aqueous K_2CO_3 and water. The organic phase was dried over MgSO_4 , then evaporated to give 6.88 g (55%) of ethyl 3-cyclopropyl-2-oxopropanoate as a yellow oil. ^1H NMR (CDCl_3): δ 4.29 (2H, q, $J = 8$ Hz), 2.71 (2H, d, $J = 9$ Hz), 1.35 (3H, t, $J = 8$ Hz), 1.05-0.98 (1H, m), 0.59-0.54 (2H, m), 0.17-0.14 (2H, m).

Step 4. To a solution of ethyl 3-cyclopropyl-2-oxopropanoate (4.75 g, 30.44 mmol) in CCl₄ (60 mL) at rt was added NBS (5.96 g 33.49 mmol). The resulting mixture was heated at reflux overnight, then cooled, filtered, and evaporated to provide ethyl 3-bromo-3-cyclopropyl-2-oxopropanoate; ¹H NMR (CDCl₃): δ 4.46-4.32 (3H, m), 1.41 (3H, t, J = 8 Hz), 0.96-0.86 (1H, m), 0.55-0.50 (2H, m), 0.07-0.03 (2H, m). This compound was used without purification for the preparation of compounds of the invention such as 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-cyclopropyl-1H-imidazole-4-carboxamide hydrochloride (Table entry 22). In a similar manner, ethyl 3-bromo-3-cyclobutyl-2-oxopropanoate and ethyl 3-bromo-3-isobutyl-2-oxopropanoate were prepared.

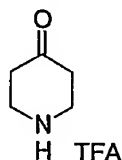
Intermediate C

Ethyl 3-bromo-2-oxoheptanoate



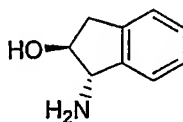
Step 1. To a suspension of LiI (23.61 g, 176.44 mmol) in THF (200 mL) at rt was slowly added Cu₂Br₂ (25.30 g, 88.22 mmol). A vigorous exothermic reaction occurred, and the mixture was then cooled to -78°C. Pentylmagnesium bromide (2M, 36.76 mL, 88.22 mmol) was slowly added at -78°C, and followed soon after by ethyl chloro(oxo)acetate (10g, 73.52 mmol). The resulting solution was stirred 10 minutes at -78°C, then quenched by dropwise addition of water. The mixture was allowed to warm to rt, and then the organic phase was separated, dried (MgSO₄), and evaporated. Purification by flash chromatography using 9:1 hexane/EtOAc as eluant gave ethyl 2-oxoheptanoate as a colorless oil (3.0 g, 23%). ¹H NMR (400 MHz, CDCl₃) δ 4.33-4.21 (m, 2 H), 2.82 (m, 2 H), 1.63-1.59 (m, 2 H), 1.63-1.19 (m, p H), 0.9-0.83 (m, 3 H), LC-MS *m/z* 279.21 (MH⁺), retention time 2.42 min (method 2).

Step 2. To a cold solution of ethyl 2-oxoheptanoate (2 g, 11.62 mmol) in AcOH (20 mL), was added Br₂ (596 μL, 11.62 mmol). The mixture was stirred 20 minutes at 0°C, then the mixture was allowed to warm to rt. After the mixture was stirred for 3 h, water and CH₂Cl₂ were added. The organic phase was separated, dried (MgSO₄), and evaporated to give crude ethyl 3-bromo-2-oxoheptanoate as a dark oil; ¹H NMR (400 MHz, CDCl₃) δ 5.05-5.01 (m, 1 H), 4.45-4.20 (m, 2 H), 2.18-1.94 (m, 2 H), 1.74-1.57 (m, 2 H), 1.48-1.17 (m, 5 H), 0.95-0.82 (m, 3 H). This compound was used without purification for the preparation of compounds of the invention such as 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-butyl-1H-imidazole-4-carboxamide hydrochloride (Table entry 20).

Intermediate D4-Piperidinone trifluoroacetate

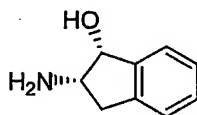
5 A suspension of t-butyl 4-oxo-1-piperidine carboxylate (10 g, 0.05 mol) in trifluoroacetic acid (10 mL) was stirred rt overnight and concentrated to give a pale yellow solid (11.26 g, crude). MS (Electron spray) 100 (MH^+), free amine; 1H NMR (300 MHz, CD_3OD) δ 3.27-3.12 (m, 4H), 2.01-1.86 (m, 4H).

10

Intermediate Etrans-1-Amino-2-hydroxyindan

15 This compound was prepared as described by Thompson et al., (J. Med. Chem. 35:1685-1701, 1992). To 1 liter of 12 N NH_4OH cooled to $0^\circ C$ was added 50 g (0.235 mol) of 2-bromo-1-indanol. After stirring for 30 minutes, the mixture was allowed to warm, and then stirred for 24 hours. The mixture was concentrated under reduced pressure to remove excess ammonia and then allowed to stand open at rt overnight. The mixture was made basic ($pH > 10$) by addition of 20% KOH, cooled in an ice bath, and filtered. After the residue was dried in a vacuum oven at $60^\circ C$ overnight, the desired product was obtained as a tan solid (24 g, 69%).

20

Intermediate Fcis-1-Hydroxy-2-aminoindan

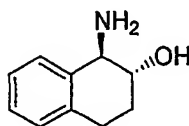
25

Following the procedure described in Tetrahedron: Asymmetry 7:1559-1562, 1996, trans-2-bromo-1-indanol (500 mg, 2.35 mmol) was dissolved in DMF (5 mL) and sodium azide (305

mg, 4.69 mmol) was added dropwise. The mixture was stirred at rt for 1 h, and then heated to 70°C and stirred for an additional 18 h. The mixture was cooled, water was added, and extracted with ether. The ether was removed and the crude (412 mg) was dissolved in THF (15 mL). This solution was added to Pd/C (41. mg) and stirred under hydrogen at rt for 3 days. The reaction mixture was filtered and the filtrate was concentrated down to provide the desired product, which was used without purification.

Intermediate G

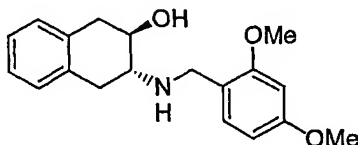
trans-1-Amino-2-hydroxy-1,2,3,4-tetrahydronaphthalene



This compound was prepared from dihydronaphthalene according to the procedures described by Bellucci et al., (Tetrahedron: Asymmetry 8:895-902, 1997).

Intermediate H

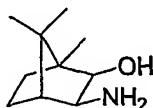
trans-(2R,3R)-3-[(2,4-Dimethoxybenzyl)amino]-1,2,3,4-tetrahydro-2-naphthalenol



This compound was prepared by following the procedure described by Efange et al., (J. Med. Chem. 40:3905-3914, 1997).

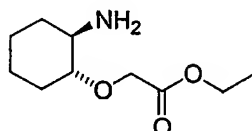
Intermediate I

(1S,2R,3S,4R)-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol



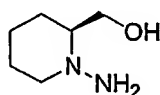
This compound, and its enantiomer, were obtained by LiAlH_4 reduction of the respective camphorquinone 3-oximes, by the procedure described by Gawley and Zhang, (J. Org. Chem. 61:8103-8112, 1996).

5

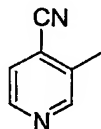
Intermediate JEthyl [(trans-2-aminocyclohexyl)oxy]acetate

10 To a solution of trans-2-amino-cyclohexanol hydrochloride (455 mg, 3.0 mmol) in THF (7 mL) was added sodium hydride (78 mg, 3.25 mmol) under argon. The mixture was stirred at rt for 12 h before ethyl bromoacetate (500 mg, 3.0 mmol) was added, and the solution was stirred at rt for another 12 h. After filtration, the solution was concentrated and the residue taken up in CH_2Cl_2 and washed with brine. The organic layer was separated and concentrated. The residue was
15 purified by flash chromatography over silica gel (ethyl acetate) to afford the desired product (51 mg, 8.5% yield): LC-MS m/z 202.2 (MH^+), retention time 0.73 min (method 1); R_f = 0.23 (ethyl acetate).

20

Intermediate K[(2S)-1-Amino-2-piperidinyl]methanol

25 [(2S)-1-Amino-2-piperidinyl]methanol was prepared according to the method described by Rosling et al., (Heterocycles 95-106, 1997). In a similar manner were prepared [(2R)-1-amino-2-piperidinyl]-methanol, [(2S)-1-amino-2-pyrrolidinyl]methanol, and [(2R)-1-amino-2-pyrrolidinyl]methanol.

Intermediate L3-Methylisonicotinonitrile

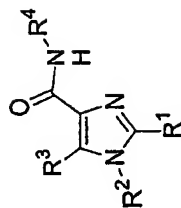
5 This nitrile was synthesized the procedure described by van den Haak et al., (J. Heterocycl. Chem. 18:1349-1352, 1981.

Summary of Examples

10 Using appropriate starting materials and the experimental procedures described above for Examples 1-49 and Intermediates A-L, the following compounds in Tables 1-18 were prepared. It will be understood by those skilled in the art that some minor modifications to the referenced procedures may have been made, but such modifications do not significantly affect the results of the preparation.

15 LC-MS characterization of compounds, as listed in the tables, was carried out by using the instrumentation and methods set forth above.

Table 1



| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC R _f (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------|---|---------------------------|------------------------------|---------------|-------------|-----------------------------|
| 1 | 2,3-Cl ₂ -Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2,3-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 449.1 | | 3.05 | 1 | 8 |
| 2 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 449.3 | 0.47 (EtOAc) | 3.14 | 1 | 13, 14 |
| 3 | 2,4-Cl ₂ -Ph | 4-F-Ph | H | 1-piperidinyl | 1-(4-fluorophenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 433.3 | 0.20 (33% EtOAc in Hexane) | 2.89 | 1 | 15 |
| 4 | 2,4-Cl ₂ -Ph | 4-I-Ph | H | 1-piperidinyl | 1-(4-iodophenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 541.0 | | 3.24 | 1 | 13, 14 |
| 5 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | 1-piperidinyl | 1-(4-methoxyphenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 445.3 | 0.53 (EtOAc) | 2.92 | 1 | 10 |

Table 1

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------|---|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 6 | 2,4-Cl ₂ -Ph | 4-Me-Ph | H | 1-piperidinyl | 1-(4-methylphenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 429.3 | 0.25 (75% EtOAc in Hexane) | 2.96 | 1 | 15 |
| 7 | 2,4-F ₂ -Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2,4-difluorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 417.2 | 0.35 (EtOAc) | 2.80 | 1 | 8 |
| 8 | 2,4-Me ₂ -Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 409.3 | 0.62 (EtOAc) | 2.77 | 1 | 10 |
| 9 | 2,4-Me ₂ -Ph | 4-Cl-Ph | Me | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-5-methyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 423.2 | | 2.89 | 1 | 8 |
| 10 | 2,5-Cl ₂ -Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2,5-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 449.1 | 0.34 (75% EtOAc in Hexane) | 3.11 | 1 | 8 |
| 11 | 2-CF ₃ -Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-N-(1-piperidinyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carboxamide hydrochloride | 449.3 | 0.25 (90% EtOAc in Hexane) | 2.95 | 1 | 13, 14 |
| 12 | 2-Cl-4-F-Ph | 4-F-Ph | H | 1-piperidinyl | 1-(4-fluorophenyl)-2-(2-chloro-4-fluorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 417.3 | 0.33 (EtOAc) | 2.69 | 1 | 10 |

Table 1

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|------------------------|----------------|----------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 13 | 2-Cl-Ph | 2,4-F ₂ -Ph | H | 1-piperidinyl | 1-(2,4-difluorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 417.2 | 0.18 (1:1 EtOAc/Hexane) | 2.64 | 1 | 13,14 |
| 14 | 2-Cl-Ph | 2-Cl-4-F-Ph | H | 1-piperidinyl | 1-(2-chloro-4-fluorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 433.2 | 0.20 (1:1 EtOAc/Hexane) | 2.74 | 1 | 13,14 |
| 15 | 2-Cl-Ph | 3-Cl-Ph | H | 1-piperidinyl | 1-(3-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 415.8 | 0.15 (50% EtOAc in Hexane) | 2.90 | 1 | 13,14 |
| 16 | 2-Cl-Ph | 3-Cl-Ph | Pr | 1-piperidinyl | 1-(3-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-propyl-1H-imidazole-4-carboxamide | 457.2 | 0.37 (1:1 EtOAc/Hexane) | 2.98 | 1 | 13,14 |
| 17 | 2-Cl-Ph | 4-Br-Ph | Et | 1-piperidinyl | 1-(4-bromophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide | 487.2 | 0.48 (EtOAc) | 3.05 | 1 | 13,14 |
| 18 | 2-Cl-Ph | 4-Br-Ph | Pr | 1-piperidinyl | 1-(4-bromophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-propyl-1H-imidazole-4-carboxamide | 503.1 | 0.28 (1:1 EtOAc/Hexane) | 3.06 | 1 | 13,14 |
| 19 | 2-Cl-Ph | 4-Cl-Ph | Br | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-bromo-1H-imidazole-4-carboxamide hydrochloride | 493.0 | | 2.64 | 2 | 13,14 |

Table 1

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|--------------------------------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 20 | 2-Cl-Ph | 4-Cl-Ph | Bu | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-butyl-1H-imidazole-4-carboxamide hydrochloride | 471.3 | | 2.88 | 2 | 13,14 |
| 21 | 2-Cl-Ph | 4-Cl-Ph | Cl | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-chloro-1H-imidazole-4-carboxamide | 451.2 | 0.16 (50% EtOAc in Hexane) | 3.07 | 1 | 10 |
| 22 | 2-Cl-Ph | 4-Cl-Ph | cyclopropyl | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-cyclopropyl-1H-imidazole-4-carboxamide hydrochloride | 455.2 | | 2.94 | 2 | 13,14 |
| 23 | 2-Cl-Ph | 4-Cl-Ph | Et | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide | 443.6 | 0.21 (60% EtOAc in Hexane) | 2.91 | 1 | 8 |
| 24 | 2-Cl-Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 415.1 | 0.25 (75% EtOAc in Hexane) | 2.88 | 1 | 13,14 |
| 25 | 2-Cl-Ph | 4-Cl-Ph | H | 2,6-dimethyl-1-piperidinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2,6-dimethyl-1-piperidinyl)-1H-imidazole-4-carboxamide | 443.3 | 0.20 (50% EtOAc in Hexane) | 2.94 | 1 | 13,14 |
| 26 | 2-Cl-Ph | 4-Cl-Ph | H | (2S)-2-(hydroxymethyl)-1-piperidinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2S)-2-(hydroxymethyl)-1-piperidinyl]-1H-imidazole-4-carboxamide | 445.1 | 0.37 (EtOAc) | 2.93 | 1 | 8 |

Table 1

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|-------------------|----------------|--------------------------------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 27 | 2-Cl-Ph | 4-Cl-Ph | H | (2R)-2-(hydroxymethyl)-1-piperidinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2R)-2-(hydroxymethyl)-1-piperidinyl]-1H-imidazole-4-carboxamide | 445.6 | 0.40 (0.2% MeOH in EtOAc) | 2.94 | 1 | 13,14 |
| 28 | 2-Cl-Ph | 4-Cl-Ph | iPr | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-isopropyl-1H-imidazole-4-carboxamide hydrochloride | 457.2 | | 3.23 | 2 | 13,14 |
| 29 | 2-Cl-Ph | 4-Cl-Ph | Me | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-methyl-1H-imidazole-4-carboxamide | 429.2 | 0.33 (EtOAc) | 2.97 | 1 | 6 |
| 30 | 2-Cl-Ph | 4-Cl-Ph | Pr | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-propyl-1H-imidazole-4-carboxamide | 457.7 | 0.2 (40% EtOAc in Hexane) | 3.04 | 1 | 8 |
| 31 | 2-Cl-Ph | 4-EtNHCO NH-Ph | Me | 1-piperidinyl | 2-(2-chlorophenyl)-1-(4-[[[(ethylamino)carbonyl]amino]phenyl]-5-methyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide trifluoroacetate | 481.4 | | 2.35 | 1 | 46 |
| 32 | 2-Cl-Ph | 4-F-Ph | H | 1-piperidinyl | 1-(4-fluorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 399.3 | 0.15 (50% EtOAc in Hexane) | 2.61 | 1 | 13,14 |
| 33 | 2-Cl-Ph | 4-F-Ph | Pr | 1-piperidinyl | 1-(4-fluorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-propyl-1H-imidazole-4-carboxamide | 441.2 | 0.23 (1:1 EtOAc/Hexane) | 2.84 | 1 | 13,14 |

Table 1

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------------------|----------------|----------------|---|---------------------------|-------------------------|---------------|-------------|-----------------------------|
| 34 | 2-Cl-Ph | 4-IPr-Ph | Et | 1-piperidinyl | 1-(4-isopropylphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide | 451.2 | 0.4 (2:1 EtOAc/Hexane) | 3.06 | 1 | 13,14 |
| 35 | 2-Cl-Ph | 4-MeCON H-Ph | Me | 1-piperidinyl | 1-[4-(acetylamino)phenyl]-2-(2-chlorophenyl)-5-methyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide trifluoroacetate | 452.3 | | 2.31 | 1 | 47 |
| 36 | 2-Cl-Ph | 4-MeO-Ph | H | 1-piperidinyl | 1-(4-methoxyphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 411.3 | 0.29 (EtOAc) | 2.62 | 1 | 13,14 |
| 37 | 2-Cl-Ph | 4-MeO-Ph | Pr | 1-piperidinyl | 1-(4-methoxyphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-propyl-1H-imidazole-4-carboxamide | 453.1 | 0.19 (1:1 EtOAc/Hexane) | 2.84 | 1 | 13,14 |
| 38 | 2-Cl-Ph | 4-Me-Ph | H | 1-piperidinyl | 1-(4-methylphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 395.3 | 0.43 (EtOAc) | 2.77 | 1 | 10 |
| 39 | 2-Cl-Ph | 4-MeSO ₂ N H-Ph | Me | 1-piperidinyl | 2-(2-chlorophenyl)-5-methyl-1-[4-[(methylsulfonyl)amino]phenyl]-N-(1-piperidinyl)-1H-imidazole-4-carboxamide trifluoroacetate | 488.4 | | 2.29 | 1 | 48 |
| 40 | 2-Cl-Ph | 4-MeSO ₂ -Ph | Me | 1-piperidinyl | 2-(2-chlorophenyl)-5-methyl-1-[4-(methylsulfonyl)phenyl]-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 473.6 | 0.25 (EtOAc) | 2.45 | 1 | 13,14 |

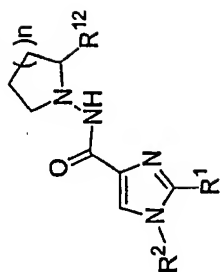
Table 1

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|-----------------------|----------------|----------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 41 | 2-Cl-Ph | 4-NO ₂ -Ph | Me | 1-piperidinyl | 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 440.3 | 0.47 (EtOAc) | 2.68 | 1 | 8 |
| 42 | 2-Cl-Ph | Ph | H | 1-piperidinyl | 2-(2-chlorophenyl)-1-phenyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 381.4 | 0.19 (75% EtOAc in Hexane) | 2.64 | 1 | 13,14 |
| 43 | 2-Et-Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-ethylphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 409.2 | 0.2 (50% EtOAc in Hexane) | 2.95 | 1 | 8 |
| 44 | 2-MeO-Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-methoxyphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 411.3 | 0.38 (75% EtOAc in Hexane) | 2.73 | 1 | 8 |
| 45 | 2-Me-Ph | 2-Me-Ph | H | 1-piperidinyl | 1-(2-methylphenyl)-2-(2-methylphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 375.4 | 0.28 (75% EtOAc in Hexane) | 2.68 | 1 | 13,14 |
| 46 | 2-Me-Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-methylphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 395.3 | 0.56 (EtOAc) | 2.83 | 1 | 8 |
| 47 | 2-Me-Ph | 4-Me-Ph | H | 1-piperidinyl | 1-(4-methylphenyl)-2-(2-methylphenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 375.4 | 0.17 (50% EtOAc in Hexane) | 2.66 | 1 | 13,14 |

Table 1

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC R _f (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. . |
|-----------|-----------------------|-------------------------|----------------|----------------|--|---------------------------|------------------------------|---------------|-------------|-------------------------------|
| 48 | 2-NO ₂ -Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-nitrophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 426.4 | 0.20 (80% EtOAc in Hexane) | 2.60 | 1 | 13, 14 |
| 49 | 4-Br-Ph | 2,4-Cl ₂ -Ph | H | 1-piperidinyl | 2-(4-bromophenyl)-1-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 495.0 | | 3.23 | 1 | 13, 14 |
| 50 | 4-Cl-Ph | 2,4-Cl ₂ -Ph | H | 1-piperidinyl | 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide hydrochloride | 451.1 | | 3.19 | 1 | 13, 14 |
| 51 | 4-I-Ph | 2,4-Cl ₂ -Ph | H | 1-piperidinyl | 2-(4-iodophenyl)-1-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 541.0 | | 3.30 | 1 | 13, 14 |
| 52 | Ph | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-phenyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 381.3 | | 2.65 | 1 | 8 |
| 53 | Ph | Ph | H | 1-piperidinyl | 1,2-diphenyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 347.2 | | 3.50 | 1 | 13, 14 |

Table 2



| Entry No. | R ¹ | R ² | n | R ¹² | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|---|-------------------------|---|---------------------------|---------------------------|----------------|-------------|-----------------------------|
| 54 | 2-MeO-Ph | 4-Cl-Ph | 1 | H | 1-(4-chlorophenyl)-2-(2-methoxyphenyl)-N-(1-pyrrolidinyl)-1H-imidazole-4-carboxamide | 397.3 | 0.2 (75% EtOAc in hexane) | 2.46 | 1 | 13,14 |
| 55 | 2-Cl-Ph | 4-Cl-Ph | 1 | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1-pyrrolidinyl)-1H-imidazole-4-carboxamide trifluoroacetate | 401.2 | 0.4 (5% MeOH in EtOAc) | 2.55 | 1 | 8 |
| 56 | 2-Cl-Ph | 4-Cl-Ph | 1 | (R)-CH ₂ OMe | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide trifluoroacetate | 445.2 | 0.4 (35% EtOAc in hexane) | 2.84 | 1 | 8 |
| 57 | 2-Cl-Ph | 4-Cl-Ph | 1 | (S)-CH ₂ OMe | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide trifluoroacetate | 445.2 | 0.4 (5% MeOH in EtOAc) | 2.89 | 1 | 8 |

Table 2

| Entry No. | R ¹ | R ² | n | R ¹² | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|---|-------------------------|---|---------------------------|---------------------------|----------------|-------------|-----------------------------|
| 58 | 2-MeO-Ph | 4-Cl-Ph | 1 | (R)-CH ₂ OMe | 1-(4-chlorophenyl)-N-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-2-(2-methoxyphenyl)-1H-imidazole-4-carboxamide | 441.3 | 0.25 (EtOAc) | 2.72 | 1 | 13,14 |
| 59 | 2-MeO-Ph | 4-Cl-Ph | 1 | (S)-CH ₂ OMe | 1-(4-chlorophenyl)-N-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-2-(2-methoxyphenyl)-1H-imidazole-4-carboxamide | 441.3 | 0.25 (EtOAc) | 2.73 | 1 | 13,14 |
| 60 | 2-MeO-Ph | 4-Cl-Ph | 3 | H | N-(1-azepanyl)-1-(4-chlorophenyl)-2-(2-methoxyphenyl)-1H-imidazole-4-carboxamide | 425.3 | 0.5 (50% EtOAc in hexane) | 2.72 | 1 | 13,14 |
| 61 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | 1 | H | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(1-pyrrolidinyl)-1H-imidazole-4-carboxamide trifluoroacetate | 435.1 | 0.36 (EtOAc) | 2.78 | 1 | 13,14 |
| 62 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | 1 | (R)-CH ₂ OMe | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide trifluoroacetate | 479.2 | 0.36 (EtOAc) | 3.13 | 1 | 13,14 |
| 63 | 2-Me-Ph | 4-Cl-Ph | 1 | H | 1-(4-chlorophenyl)-2-(2-methylphenyl)-N-(1-pyrrolidinyl)-1H-imidazole-4-carboxamide | 381.3 | 0.2 (EtOAc) | 2.48 | 1 | 13,14 |

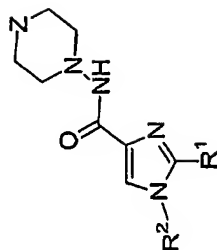
Table 2

| Entry No. | R ¹ | R ² | n | R ¹² | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|---|-------------------------|--|---------------------------|------------------|----------------|-------------|-----------------------------|
| 64 | 2-Me-Ph | 4-Cl-Ph | 1 | (R)-CH ₂ OMe | 1-(4-chlorophenyl)-N-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-2-(2-methylphenyl)-1H-imidazole-4-carboxamide | 425.3 | 0.33 (EtOAc) | 2.78 | 1 | 13,14 |
| 65 | 2-Me-Ph | 4-Cl-Ph | 1 | (S)-CH ₂ OMe | 1-(4-chlorophenyl)-N-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-2-(2-methylphenyl)-1H-imidazole-4-carboxamide | 425.3 | 0.33 (EtOAc) | 2.79 | 1 | 13,14 |
| 66 | 2-Me-Ph | 4-Cl-Ph | 3 | H | N-(1-azepanyl)-1-(4-chlorophenyl)-2-(2-methylphenyl)-1H-imidazole-4-carboxamide | 409.3 | 0.57 (EtOAc) | 2.82 | 1 | 13,14 |
| 67 | 2,4-Me ₂ -Ph | 4-Cl-Ph | 1 | H | 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(1-pyrrolidinyl)-1H-imidazole-4-carboxamide | 395.3 | 0.25 (EtOAc) | 2.61 | 1 | 13,14 |
| 68 | 2,4-Me ₂ -Ph | 4-Cl-Ph | 1 | (R)-CH ₂ OMe | 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide | 439.3 | 0.32 (EtOAc) | 2.90 | 1 | 13,14 |
| 69 | 2,4-Me ₂ -Ph | 4-Cl-Ph | 1 | (S)-CH ₂ OMe | 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide | 439.3 | 0.32 (EtOAc) | 2.91 | 1 | 13,14 |

Table 2

| Entry No. | R ¹ | R ² | n | R ¹² | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|---|-------------------------|--|---------------------------|---------------------------|----------------|-------------|-----------------------------|
| 70 | 2,4-Me ₂ -Ph | 4-Cl-Ph | 3 | H | N-(1-azepanyl)-1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-1H-imidazole-4-carboxamide | 423.3 | 0.6 (EtOAc) | 2.93 | 1 | 13,14 |
| 71 | 2,4-Cl ₂ -Ph | 4-Me-Ph | 3 | H | N-(1-azepanyl)-2-(2,4-dichlorophenyl)-1-(4-methylphenyl)-1H-imidazole-4-carboxamide trifluoroacetate | 443.3 | 0.4 (75% EtOAc in hexane) | 3.03 | 1 | 15 |
| 72 | 2,4-Cl ₂ -Ph | 4-F-Ph | 3 | H | N-(1-azepanyl)-2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazole-4-carboxamide trifluoroacetate | 447.3 | 0.4 (75% EtOAc in hexane) | 2.96 | 1 | 15 |
| 73 | 2-Cl-Ph | 4-Cl-Ph | 1 | (S)-CH ₂ OMe | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2S)-2-(hydroxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide | 431.1 | 0.24 (EtOAc) | 2.81 | 1 | 8 |
| 74 | 2-Cl-Ph | 4-Cl-Ph | 1 | (R)-CH ₂ OMe | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(2R)-2-(hydroxymethyl)-1-pyrrolidinyl]-1H-imidazole-4-carboxamide | 431.2 | 0.35 (EtOAc) | 2.71 | 1 | 13,14 |

Table 3



| Entry No. | R ¹ | R ² | Z | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|---|--|---------------------------|--|----------------|-------------|-----------------------------|
| 75 | 2-Cl-Ph | 4-Cl-Ph | O | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide | 417.0 | 0.45 (7% MeOH in CH ₂ Cl ₂) | 3.32 | 1 | 8 |
| 76 | 2-MeO-Ph | 4-Cl-Ph | O | 1-(4-chlorophenyl)-2-(2-methoxyphenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide | 413.2 | 0.22 (75% EtOAc in hexane) | 2.55 | 1 | 13, 14 |
| 77 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | O | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide | 453.2 | 0.57 (50% EtOAc in hexane) | 3.03 | 1 | 13, 14 |
| 78 | 2,4-F-Ph | 4-Cl-Ph | O | 1-(4-chlorophenyl)-2-(2,4-difluorophenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide | 419.2 | 0.28 (5% MeOH in EtOAc) | 2.73 | 1 | 8 |

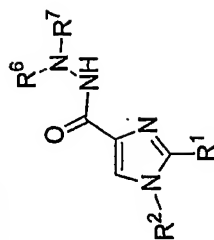
Table 3

| Entry No. | R ¹ | R ² | Z | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|-----|---|---------------------------|---|----------------|-------------|-----------------------------|
| 79 | 2-Me-Ph | 4-Cl-Ph | O | 1-(4-chlorophenyl)-2-(2-methylphenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide | 397.3 | 0.18 (EtOAc) | 2.63 | 1 | 13, 14 |
| 80 | 2,4-Me-Ph | 4-Cl-Ph | O | 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(4-morpholinyl)-1H-imidazole-4-carboxamide | 411.3 | 0.19 (EtOAc) | 2.77 | 1 | 13, 14 |
| 81 | 2,4-Me-Ph | 4-Cl-Ph | NMe | 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(4-methyl-1-piperazinyl)-1H-imidazole-4-carboxamide bis(trifluoroacetate) | 421.2 | 0.6 (20% 2M NH ₃ /MeOH in EtOAc) | 2.82 | 1 | 13, 14 |
| 82 | 2,4-Cl ₂ -Ph | 4-Me-Ph | NMe | 2-(2,4-dichlorophenyl)-1-(4-methylphenyl)-N-(4-methyl-1-piperazinyl)-1H-imidazole-4-carboxamide bis(trifluoroacetate) | 444.3 | | 2.29 | 1 | 15 |
| 83 | 2,4-Cl ₂ -Ph | 4-F-Ph | NMe | 2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-N-(4-methyl-1-piperazinyl)-1H-imidazole-4-carboxamide bis(trifluoroacetate) | 448.2 | | 2.21 | 1 | 15 |

Table 3

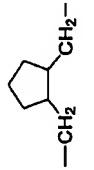
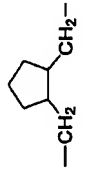
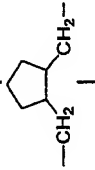
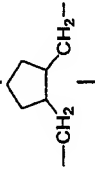
| Entry No. | R ¹ | R ² | Z | IUPAC name | MS m/z [MH ⁺] | TLC R _f (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|-----|--|---------------------------|--|----------------|-------------|-----------------------------|
| 84 | 2-Et-Ph | 4-Cl-Ph | NMe | 1-(4-chlorophenyl)-2-(2-ethylphenyl)-N-(4-methyl-1-piperazinyl)-1H-imidazole-4-carboxamide | 424.3 | 0.62 (25% 2M NH ₃ /MeOH in EtOAc) | 2.28 | 1 | 13, 14 |

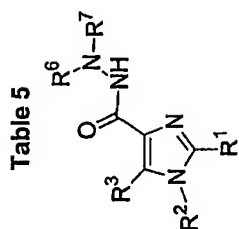
Table 4



| Entry No. | R ¹ | R ² | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | HPLC Retention time (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------|---|---------------------------|----------------------------|-------------|-----------------------------|
| 85 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | Me | Me | 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N,N'-dimethyl-1H-imidazole-4-carbohydrazide | 409.0 | 2.9 | 1 | 8 |
| 86 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | | | 2-(2,4-dichlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide hydrochloride | 471 | 2.98 | 2 | 10,11,12 |
| 87 | 2-Me-Ph | 4-Cl-Ph | | | 1-(4-chlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-2-(2-methylphenyl)-1H-imidazole-4-carboxamide hydrochloride | 421 | 2.82 | 2 | 10,11,12 |
| 88 | 2,4-Cl ₂ -Ph | 4-F-Ph | | | 2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-1H-imidazole-4-carboxamide hydrochloride | 459 | 3.38 | 2 | 10,11,12 |

Table 4

| Entry No. | R ¹ | R ² | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | HPLC Retention time (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|---|---|--|---------------------------|----------------------------|-------------|-----------------------------|
| 89 | 2,4-Cl ₂ -Ph | 4-Cl-Ph |  |  | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-1H-imidazole-4-carboxamide hydrochloride | 475 | 3.16 | 2 | 10,11,12 |
| 90 | 2-Cl-Ph | 4-Cl-Ph |  |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-1H-imidazole-4-carboxamide hydrochloride | 441 | 3.23 | 2 | 10,11,12 |



| Entry No. | R ¹ | R ² | R ³ | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|-----------------------|----------------|--|---------------------------|---------------------------|---------------|-------------|-----------------------------|
| 91 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 2-CF ₃ -Ph | H | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide | 525 | 0.4 (20% EtOAc/Hexane) | 4.25 | 2 | 10,11,12 |
| 92 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | Ph | Me | 2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide | 473 | 0.6 (50% EtOAc in Hexane) | 3.70 | 1 | 8 |
| 93 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 3-Cl-4-F-Ph | H | N'-(3-chloro-4-fluorophenyl)-2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 509 | | 4.13 | 2 | 10,11,12 |
| 94 | 2,4-Cl ₂ -Ph | 4-F-Ph | H | 2-Cl-Ph | H | N'-(2-chlorophenyl)-2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 475 | | 3.40 | 2 | 10,11,12 |

Table 5

| Entry No. | R ¹ | R ² | R ³ | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------------------|----------------|---|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 95 | 2,4-Cl ₂ -Ph | 4-F-Ph | H | 3-Cl-4-F-Ph | H | N'-(3-chloro-4-fluorophenyl)-2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 493 | | 3.39 | 2 | 10,11,12 |
| 96 | 2,4-Cl ₂ -Ph | 4-F-Ph | H | 2-Cl-4-CF ₃ -Ph | H | N'-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 543 | | 3.66 | 2 | 10,11,12 |
| 97 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | 3-Cl-4-F-Ph | H | N'-(3-chloro-4-fluorophenyl)-2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 505 | | 3.36 | 2 | 10,11,12 |
| 98 | 2,4-F ₂ -Ph | 4-Cl-Ph | H | Ph | Me | 1-(4-chlorophenyl)-2-(2,4-difluorophenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide | 439 | 0.27 (50% EtOAc in Hexane) | 3.39 | 1 | 8 |
| 99 | 2,4-Me ₂ -Ph | 4-Cl-Ph | H | Ph | Me | 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide | 431 | 0.64 (50% EtOAc in Hexane) | 3.48 | 1 | 8 |

Table 5

| Entry No. | R ¹ | R ² | R ³ | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|-----------------------|----------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 100 | 2,5-Cl ₂ -Ph | 4-Cl-Ph | H | 2-CF ₃ -Ph | H | 1-(4-chlorophenyl)-2-(2,5-dichlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide | 525 | 0.41 (25% EtOAc in Hexane) | 3.76 | 1 | 8 |
| 101 | 2,5-Cl ₂ -Ph | 4-Cl-Ph | H | 3-CF ₃ -Ph | H | 1-(4-chlorophenyl)-2-(2,5-dichlorophenyl)-N'-[3-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide | 526 | 0.2 (33% EtOAc in Hexane) | 3.69 | 1 | 8 |
| 102 | 2,5-Cl ₂ -Ph | 4-Cl-Ph | H | 4-CF ₃ -Ph | H | 1-(4-chlorophenyl)-2-(2,5-dichlorophenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide | 526 | 0.2 (33% EtOAc in Hexane) | 3.70 | 1 | 8 |
| 103 | 2-CF ₃ -Ph | 4-Cl-Ph | H | 4-CF ₃ -Ph | H | 1-(4-chlorophenyl)-2-[2-(trifluoromethyl)phenyl]-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide trifluoroacetate | 525 | | 3.38 | 2 | 10,11,12 |
| 104 | 2-CF ₃ -Ph | 4-Cl-Ph | H | 2-CF ₃ -Ph | H | 1-(4-chlorophenyl)-N',2-bis[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride | 525 | | 3.97 | 2 | 10,11,12 |

Table 5

| Entry No. | R ¹ | R ² | R ³ | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------------------|----------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 105 | 2-Cl-Ph | 4-Br-Ph | Et | 2-CF ₃ -Ph | H | 1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide | 563 | 0.24 (20% EtOAc in Hexane) | 3.88 | 1 | 8 |
| 106 | 2-Cl-Ph | 4-Br-Ph | Et | 4-CF ₃ -Ph | H | 1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide | 563 | 0.27 (33% EtOAc in Hexane) | 3.82 | 1 | 8 |
| 107 | 2-Cl-Ph | 4-Br-Ph | Et | 2-Cl-4-CF ₃ -Ph | H | 1-(4-bromophenyl)-2-(2-chlorophenyl)-N'-[2-chloro-4-(trifluoromethyl)phenyl]-5-ethyl-1H-imidazole-4-carbohydrazide | 597 | 0.18 (20% EtOAc in Hexane) | 3.98 | 1 | 6 |
| 108 | 2-Cl-Ph | 4-Cl-Ph | Cyclopropyl | 2-CF ₃ -Ph | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-cyclopropyl-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride | 531 | | 3.61 | 2 | 13,14 |
| 109 | 2-Cl-Ph | 4-Cl-Ph | Cyclopropyl | 4-CF ₃ -Ph | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-cyclopropyl-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride | 531 | | 3.62 | 2 | 13,14 |

Table 5

| Entry No. | R ¹ | R ² | R ³ | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|---|----------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 110 | 2-Cl-Ph | 4-Cl-Ph | Et | 2,4-Cl ₂ -Ph | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-ethyl-1H-imidazole-4-carbohydrazide | 519 | 0.6 (33% EtOAc in Hexane) | 4.02 | 1 | 6 |
| 111 | 2-Cl-Ph | 4-Cl-Ph | Et | 2,4-(CF ₃) ₂ -Ph | H | N'-(2,4-bis(trifluoromethyl)phenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazole-4-carbohydrazide | 587 | 0.47 (30% EtOAc in Hexane) | 3.75 | 1 | 8 |
| 112 | 2-Cl-Ph | 4-Cl-Ph | H | 2-CF ₃ -Ph | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2-(trifluoromethyl)phenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 491 | | 4.02 | 2 | 10,11,12 |
| 113 | 2-Cl-Ph | 4-Cl-Ph | H | 3-CF ₃ -Ph | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(3-(trifluoromethyl)phenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 491 | | 3.99 | 2 | 10,11,12 |
| 114 | 2-Cl-Ph | 4-Cl-Ph | H | 4-CF ₃ -Ph | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(4-(trifluoromethyl)phenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 491 | | 3.99 | 2 | 10,11,12 |

Table 5

| Entry No. | R ¹ | R ² | R ³ | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------------------|----------------|---|---------------------------|---------------------------|---------------|-------------|-----------------------------|
| 115 | 2-Cl-Ph | 4-Cl-Ph | H | 2-CF ₃ -4-Cl-Ph | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-chloro-2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride | 525 | | 3.55 | 2 | 10,11,12 |
| 116 | 2-Cl-Ph | 4-Cl-Ph | H | Ph | Me | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide | 437 | 0.5 (60% EtOAc in Hexane) | 3.85 | 1 | 8 |
| 117 | 2-Cl-Ph | 4-Cl-Ph | H | Ph | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-phenyl-1H-imidazole-4-carbohydrazide hydrochloride | 423 | | 3.07 | 2 | 10,11,12 |
| 118 | 2-Cl-Ph | 4-Cl-Ph | H | 2,4-Cl ₂ -Ph | H | N'-(2,4-dichlorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 492 | | 3.55 | 2 | 10,11,12 |
| 119 | 2-Cl-Ph | 4-Cl-Ph | H | 2,4-F ₂ -Ph | H | N'-(2,4-difluorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 460 | | 3.07 | 2 | 10,11,12 |

Table 5

| Entry No. | R ¹ | R ² | R ³ | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|---|----------------|---|---------------------------|------------------|---------------|-------------|-----------------------------|
| 120 | 2-Cl-Ph | 4-Cl-Ph | H | 2-Cl-4-CN-Ph | H | N'-(2-chloro-4-cyanophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 482 | | 3.03 | 2 | 10,11,12 |
| 121 | 2-Cl-Ph | 4-Cl-Ph | H | 2-Cl-Ph | H | N'-(2-chlorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 457 | | 3.18 | 2 | 10,11,12 |
| 122 | 2-Cl-Ph | 4-Cl-Ph | H | 3-Cl-4-F-Ph | H | N'-(3-chloro-4-fluorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 475 | | 3.28 | 2 | 10,11,12 |
| 123 | 2-Cl-Ph | 4-Cl-Ph | H | 2-Me-4-Cl-Ph | H | N'-(4-chloro-2-methylphenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 471 | | 3.36 | 2 | 10,11,12 |
| 124 | 2-Cl-Ph | 4-Cl-Ph | H | 2,4-(CF ₃) ₂ -Ph | H | N'-(2,4-bis(trifluoromethyl)phenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 559 | | 3.62 | 2 | 10,11,12 |

Table 5

| Entry No. | R ¹ | R ² | R ³ | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|---|----------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 125 | 2-Cl-Ph | 4-Cl-Ph | H | 2-Cl-4-CF ₃ -Ph | H | N'-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 525 | | 3.55 | 2 | 10,11,12 |
| 126 | 2-Cl-Ph | 4-Cl-Ph | Me | 2,4-Cl ₂ -Ph | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carbohydrazide | 505 | 0.71 (50% EtOAc in Hexane) | 3.88 | 1 | 6 |
| 127 | 2-Cl-Ph | 4-Cl-Ph | Pr | 2,4-Cl ₂ -Ph | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-propyl-1H-imidazole-4-carbohydrazide | 533 | | 3.87 | 2 | 10,11,12 |
| 128 | 2-Cl-Ph | 4-Cl-Ph | Pr | 2,4-Cl ₂ -Ph | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-propyl-1H-imidazole-4-carbohydrazide hydrochloride | 533 | | 3.87 | 2 | 10,11,12 |
| 129 | 2-Cl-Ph | 4-Cl-Ph | Pr | 2,4-(CF ₃) ₂ -Ph | H | N'-[2,4-bis(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazole-4-carbohydrazide hydrochloride | 601 | | 4.00 | 2 | 10,11,12 |

Table 5

| Entry No. | R ¹ | R ² | R ³ | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|-----------------------|----------------|---|---------------------------|------------------|---------------|-------------|-----------------------------|
| 130 | 2-Cl-Ph | 4-F-Ph | H | 2-CF ₃ -Ph | H | 2-(2-chlorophenyl)-1-(4-fluorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride | 475 | | 3.68 | 2 | 10,11,12 |
| 131 | 2-Cl-Ph | 4-F-Ph | H | 4-CF ₃ -Ph | H | 2-(2-chlorophenyl)-1-(4-fluorophenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride | 475 | | 3.27 | 2 | 10,11,12 |
| 132 | 2-Cl-Ph | 4-Me-Ph | H | 2-CF ₃ -Ph | H | 2-(2-chlorophenyl)-1-(4-methylphenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide trifluoroacetate | 471 | | 4.02 | 2 | 10,11,12 |
| 133 | 2-Cl-Ph | 4-Me-Ph | H | 3-CF ₃ -Ph | H | 2-(2-chlorophenyl)-1-(4-methylphenyl)-N'-[3-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide trifluoroacetate | 471 | | 3.88 | 2 | 10,11,12 |
| 134 | 2-Cl-Ph | 4-Me-Ph | H | 4-CF ₃ -Ph | H | 2-(2-chlorophenyl)-1-(4-methylphenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride | 471 | | 3.28 | 2 | 10,11,12 |

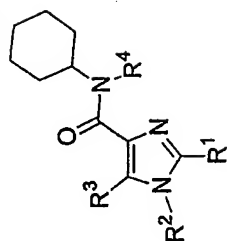
Table 5

| Entry No. | R ¹ | R ² | R ³ | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|-----------------------|----------------|-----------------------|----------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 135 | 2-Cl-Ph | 4-NO ₂ -Ph | Me | 2-CF ₃ -Ph | H | 2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide | 516 | 0.4 (33% EtOAc in Hexane) | 3.56 | 1 | 8 |
| 136 | 2-Et-Ph | 4-Cl-Ph | H | Ph | Me | 1-(4-chlorophenyl)-2-(2-ethoxyphenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide | 431 | 0.68 (50% EtOAc in Hexane) | 3.52 | 1 | 8 |
| 137 | 2-MeO-Ph | 4-Cl-Ph | H | Ph | Me | 2-(2-methoxyphenyl)-1-(4-chlorophenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide | 433 | 0.45 (50% EtOAc in Hexane) | 3.26 | 1 | 8 |
| 138 | 2-Me-Ph | 4-Cl-Ph | H | 2-CF ₃ -Ph | H | 1-(4-chlorophenyl)-2-(2-methylphenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide | 471 | 0.4 (20% EtOAc/Hexane) | 3.89 | 2 | 10,11,12 |
| 139 | 2-Me-Ph | 4-Cl-Ph | H | Ph | Me | 1-(4-chlorophenyl)-2-(2-methylphenyl)-N'-methyl-N'-phenyl-1H-imidazole-4-carbohydrazide | 417 | 0.54 (50% EtOAc in Hexane) | 3.34 | 1 | 8 |

Table 5

| Entry No. | R ¹ | R ² | R ³ | R ⁶ | R ⁷ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------|----------------|--|---------------------------|------------------|---------------|-------------|-----------------------------|
| 140 | 2-Me-Ph | 4-Cl-Ph | H | 3-Cl-4-F-Ph | H | N'-(3-chloro-4-fluorophenyl)-2-(2-methylphenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide hydrochloride | 455 | | 3.78 | 2 | 10,11,12 |

Table 6



| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|-------------------------|----------------|----------------|---|---------------------------|------------------|---------------|-------------|-----------------------------|
| 141 | 4-Br-Ph | 2,4-Cl ₂ -Ph | H | H | 2-(4-bromophenyl)-N-cyclohexyl-1-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide | 494.0 | | 3.96 | 1 | 8 |
| 142 | 4-Cl-Ph | 2,4-Cl ₂ -Ph | H | H | 2-(4-chlorophenyl)-N-cyclohexyl-1-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide | | | | | 13, 14 |
| 143 | Ph | Ph | H | H | N-cyclohexyl-1,2-diphenyl-1H-imidazole-4-carboxamide | 346.2 | | 3.22 | 1 | 8 |
| 144 | 4-I-Ph | 2,4-Cl ₂ -Ph | H | H | N-cyclohexyl-1-(2,4-dichlorophenyl)-2-(4-iodophenyl)-1H-imidazole-4-carboxamide | 540.0 | | 4.03 | 1 | 8 |

Table 6

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 145 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | H | 1-(4-chlorophenyl)-N-cyclohexyl-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide | 448.2 | 0.57 (50% EtOAc in hexane) | 3.84 | 1 | 13, 14 |
| 146 | 2-Cl-Ph | 4-Cl-Ph | H | H | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-cyclohexyl-1H-imidazole-4-carboxamide | 414.2 | 0.21 (35% EtOAc in hexane) | 3.48 | 1 | 8 |
| 147 | 2-MeO-Ph | 4-Cl-Ph | H | H | 1-(4-chlorophenyl)-N-cyclohexyl-2-(2-methoxyphenyl)-1H-imidazole-4-carboxamide | 410.2 | 0.5 (50% EtOAc in hexane) | 3.25 | 1 | 13, 14 |
| 148 | 2-Me-Ph | 4-Cl-Ph | H | H | 1-(4-chlorophenyl)-N-cyclohexyl-2-(2-methylphenyl)-1H-imidazole-4-carboxamide | 394.2 | 0.64 (50% EtOAc in hexane) | 3.44 | 1 | 13, 14 |
| 149 | 2,4-Me ₂ -Ph | 4-Cl-Ph | H | H | 1-(4-chlorophenyl)-N-cyclohexyl-2-(2,4-dimethylphenyl)-1H-imidazole-4-carboxamide | 408.3 | 0.68 (50% EtOAc in hexane) | 3.56 | 1 | 13, 14 |
| 150 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | H | N-cyclohexyl-2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 444.2 | | 3.55 | 1 | 8 |

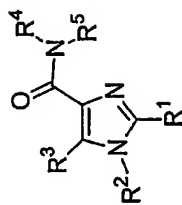
Table 6

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|-----------------------|----------------|----------------|---|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 151 | 2-F-Ph | 2-NO ₂ -Ph | Me | H | N-cyclohexyl-2-(2-fluorophenyl)-5-methyl-1-(2-nitrophenyl)-1H-imidazole-4-carboxamide | 423.2 | 0.11 (33% EtOAc in hexane) | 3.22 | 1 | 8 |
| 152 | 2,4-Cl ₂ -Ph | 4-Me-Ph | H | H | N-cyclohexyl-2-(2,4-dichlorophenyl)-1-(4-methylphenyl)-1H-imidazole-4-carboxamide | 428.2 | 0.6 (30% EtOAc in hexane) | 3.76 | 1 | 15 |
| 153 | 2,4-Cl ₂ -Ph | 4-F-Ph | H | H | N-cyclohexyl-2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazole-4-carboxamide | 432.2 | 0.17 (30% EtOAc in hexane) | 3.62 | 1 | 15 |
| 154 | 2,4-F ₂ -Ph | 4-Cl-Ph | H | H | 1-(4-chlorophenyl)-N-cyclohexyl-2-(2,4-difluorophenyl)-1H-imidazole-4-carboxamide | 416.3 | 0.22 (30% EtOAc in hexane) | 3.47 | 1 | 15 |
| 155 | 2-Cl-Ph | 4-NO ₂ -Ph | Me | H | 2-(2-chlorophenyl)-N-cyclohexyl-5-methyl-1-(4-nitrophenyl)-1H-imidazole-4-carboxamide | 439.2 | | 3.41 | 1 | 8 |
| 156 | 2-Et-Ph | 4-Cl-Ph | H | H | 1-(4-chlorophenyl)-N-cyclohexyl-2-(2-ethoxyphenyl)-1H-imidazole-4-carboxamide | 408.3 | 0.72 (50% EtOAc in hexane) | 3.62 | 1 | 13, 14 |

Table 6

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 157 | 2-Cl-Ph | 4-Cl-Ph | H | Me | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-cyclohexyl-N-methyl-1H-imidazole-4-carboxamide | 428.2 | 0.19 (50% EtOAc in hexane) | 3.47 | 1 | 8 |
| 158 | 2-Cl-Ph | 4-F-Ph | H | H | 2-(2-chlorophenyl)-N-cyclohexyl-1-(4-fluorophenyl)-1H-imidazole-4-carboxamide | 398.3 | 0.52 (50% EtOAc in hexane) | 3.22 | 1 | 10, 11, 12 |
| 159 | 2-Cl-Ph | 4-MeO-Ph | H | H | 2-(2-chlorophenyl)-N-cyclohexyl-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 410.3 | 0.47 (50% EtOAc in hexane) | 3.16 | 1 | 10, 11, 12 |
| 160 | 2-Cl-Ph | 4-Me-Ph | H | H | 2-(2-chlorophenyl)-N-cyclohexyl-1-(4-methylphenyl)-1H-imidazole-4-carboxamide | 394.3 | 0.6 (50% EtOAc in hexane) | 3.31 | 1 | 10, 11, 12 |
| 161 | Ph | 4-Cl-Ph | H | H | 1-(4-chlorophenyl)-N-cyclohexyl-2-phenyl-1H-imidazole-4-carboxamide | 380.3 | | 3.35 | 1 | 8 |
| 162 | 2,5-Cl ₂ -Ph | 4-Cl-Ph | H | H | 1-(4-chlorophenyl)-N-cyclohexyl-2-(2,5-dichlorophenyl)-1H-imidazole-4-carboxamide | 448.6 | 0.15 (25% EtOAc in hexane) | 3.83 | 1 | 8 |

Table 7



| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|-------------------------|----------------|---|----------------|---|---------------------------|---------------------------|---------------|-------------|-----------------------------|
| 163 | 4-Cl-Ph | 2,4-Cl ₂ -Ph | H | —(CH ₂) ₅ — | | 1-[(2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl]piperidine | 436.1 | | 3.59 | 1 | 13, 14 |
| 164 | 4-Cl-Ph | 2,4-Cl ₂ -Ph | H | Me | Me | 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N,N-dimethyl-1H-imidazole-4-carboxamide | | | | | 13, 14 |
| 165 | 2,4-Cl ₂ -Ph | 4-Me-Ph | H | —(CH ₂) ₅ — | | 1-[(2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl]piperidine | 414.3 | 0.2 (50% EtOAc in hexane) | 3.34 | 1 | 9 |
| 166 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | —CH ₂ CH=CH(Ph)CH ₂ CH ₂ — | | 1-[(2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl]-4-phenyl-1,2,3,6-tetrahydropyridine | 522 | | 3.53 | 2 | 10, 11, 12 |

Table 7

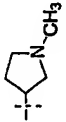
| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------|---|---|---------------------------|------------------|---------------|-------------|-----------------------------|
| 167 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | | —CH ₂ CH=CH(Ph)CH ₂ CH ₂ — | 1-[[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-phenyl-1,2,3,6-tetrahydropyridine | 526 | | 3.33 | 2 | 10, 11, 12 |
| 168 | 2-Me-Ph | 4-Cl-Ph | H | | —CH ₂ CH=CH(Ph)CH ₂ CH ₂ — | 1-[[1-(4-chlorophenyl)-2-(2-methylphenyl)-1H-imidazol-4-yl]carbonyl]-4-phenyl-1,2,3,6-tetrahydropyridine | 472 | | 2.9 | 2 | 10, 11, 12 |
| 169 | 2,4-Cl ₂ -Ph | 4-F-Ph | H | | —CH ₂ CH=CH(Ph)CH ₂ CH ₂ — | 1-[[2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazol-4-yl]carbonyl]-4-phenyl-1,2,3,6-tetrahydropyridine | 510 | | 3.05 | 2 | 10, 11, 12 |
| 170 | 2-Cl-Ph | 4-Cl-Ph | H | | —CH ₂ CH=CH(Ph)CH ₂ CH ₂ — | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-phenyl-1,2,3,6-tetrahydropyridine | 492 | | 3.47 | 2 | 10, 11, 12 |
| 171 | 2-Cl-Ph | 4-Cl-Ph | H | | —(CH ₂) ₃ CH(CH ₂ OH)CH ₂ — | (1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-3-piperidinyl)methanol | 430 | | 2.52 | 2 | 10, 11, 12 |
| 172 | 2-Cl-Ph | 4-Cl-Ph | H | Me |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-methyl-N-(1-methyl-3-pyrrolidinyl)-1H-imidazole-4-carboxamide hydrochloride | 429 | | 2.15 | 2 | 10, 11, 12 |

Table 7

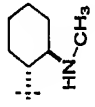
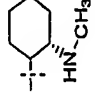
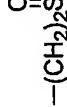
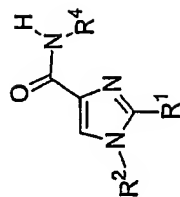
| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|--|---|---|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 173 | 2-Cl-Ph | 4-Cl-Ph | H | —(CH ₂) ₂ CH(N(Et) ₂)CH ₂ — | | N-1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-3-pyrrolidinyl)-N,N-diethylamine hydrochloride | 457 | | 2.08 | 2 | 10, 11, 12 |
| 174 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | Me |  | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-methyl-N-[(1R,2R)-2-(methylamino)cyclohexyl]-1H-imidazole-4-carboxamide hydrochloride | 491.2 | | 2.41 | 2 | 10, 11, 12 |
| 175 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | Me |  | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-methyl-N-[(1S,2S)-2-(methylamino)cyclohexyl]-1H-imidazole-4-carboxamide hydrochloride | 491.2 | | 2.34 | 2 | 10, 11, 12 |
| 176 | 2-Cl-Ph | 4-Cl-Ph | H | —(CH ₂) ₂ S(CH ₂) ₂ — | | 4-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]thiomorpholine | 418.6 | 0.3 (50% EtOAc in hexane) | 3.15 | 1 | 13, 14 |
| 177 | 2-Cl-Ph | 4-Cl-Ph | H | —(CH ₂) ₂ C(=O)(CH ₂) ₂ — | | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-piperidinone | 414.1 | 0.29 (50% EtOAc in hexane) | 2.75 | 1 | 13, 14 |
| 178 | 2-Cl-Ph | 4-Cl-Ph | H | —(CH ₂) ₂ S(CH ₂) ₂ —  | | 4-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]thiomorpholine 1-oxide | 434.5 | 0.47 (1:5 EtOAc/Hexane) | 2.55 | 1 | 13, 14 |

Table 7

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|------------------------|----------------|---|----------------|--|---------------------------|--------------------------|---------------|-------------|-----------------------------|
| 179 | 2-Cl-Ph | 4-Cl-Ph | Et | —(CH ₂) ₂ C(=O)(CH ₂) ₂ — | | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl]-4-piperidinone | 442.1 | 0.06 (1:1 EtOAc/Hexanes) | 2.99 | 1 | 13, 14 |
| 180 | 2-Cl-Ph | 4-Cl-Ph | n-Pr | —(CH ₂) ₂ C(=O)(CH ₂) ₂ — | | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl]-4-piperidinone | 456.1 | 0.06 (1:1 EtOAc/Hexanes) | 3.13 | 1 | 13, 14 |
| 181 | 2-Cl-Ph | 4-Cl-Ph | H | Me | OMe | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-methoxy-N-methyl-1H-imidazole-4-carboxamide | 376.1 | 0.22 (EtOAc) | 2.77 | 1 | 13, 14 |
| 182 | 2-Cl-Ph | 2,4-F ₂ -Ph | H | —(CH ₂) ₅ — | | 1-[[2-(2-chlorophenyl)-1-(2,4-difluorophenyl)-1H-imidazol-4-yl]carbonyl]piperidine | 402.2 | 0.36 (2:1 EtOAc/Hexanes) | 2.97 | 1 | 13, 14 |
| 183 | 2-Cl-Ph | 4- <i>i</i> -Pr-Ph | Et | —(CH ₂) ₅ — | | 1-[[2-(2-chlorophenyl)-5-ethyl-1-(4-isopropylphenyl)-1H-imidazol-4-yl]carbonyl]piperidine | 436.1 | 0.06 (1:1 EtOAc/Hexanes) | 3.36 | 1 | 13, 14 |

Table 8



| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|-----------------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 184 | 2-MeO-Ph | 4-Cl-Ph | Ph | 1-(4-chlorophenyl)-2-(2-methoxyphenyl)-N-phenyl-1H-imidazole-4-carboxamide | 404.1 | 0.83 (50% EtOAc in hexane) | 3.42 | 1 | 13, 14 |
| 185 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | Ph | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-phenyl-1H-imidazole-4-carboxamide | 444.1 | 0.89 (50% EtOAc in hexane) | 3.87 | 1 | 13, 14 |
| 186 | 2-Cl-Ph | 4-Cl-Ph | 4H-1,2,4-triazol-4-yl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4H-1,2,4-triazol-4-yl)-1H-imidazole-4-carboxamide | 399.1 | <0.1 (15% MeOH in EtOAc) | 2.71 | 1 | 8 |
| 187 | 2-Cl-Ph | 4-Cl-Ph | Ph | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-phenyl-1H-imidazole-4-carboxamide | 408.1 | 0.4 (35% EtOAc in hexane) | 3.54 | 1 | 8 |

Table 8

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|------------------------------------|---|---------------------------|--|---------------|-------------|-----------------------------|
| 188 | 2,4-F ₂ -Ph | 4-Cl-Ph | Ph | 1-(4-chlorophenyl)-2-(2,4-difluorophenyl)-N-phenyl-1H-imidazole-4-carboxamide | 410.1 | 0.5 (35% EtOAc in hexane) | 3.52 | 1 | 8 |
| 189 | 2-Me-Ph | 4-Cl-Ph | Ph | 1-(4-chlorophenyl)-2-(2-methylphenyl)-N-phenyl-1H-imidazole-4-carboxamide | 388.1 | 0.86 (50% EtOAc in hexane) | 3.52 | 1 | 13, 14 |
| 190 | 2,4-Me ₂ -Ph | 4-Cl-Ph | Ph | 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-phenyl-1H-imidazole-4-carboxamide | 402.2 | 0.92 (50% EtOAc in hexane) | 3.67 | 1 | 13, 14 |
| 191 | 2,4-Me ₂ -Ph | 4-Cl-Ph | 4H-1,2,4-triazol-4-yl | 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(4H-1,2,4-triazol-4-yl)-1H-imidazole-4-carboxamide | 393.1 | 0.19 (20% 2M NH ₃ /MeOH in EtOAc) | 2.87 | 1 | 13, 14 |
| 192 | 2,4-Me ₂ -Ph | 4-Cl-Ph | 3,5-dimethyl-4H-1,2,4-triazol-4-yl | 1-(4-chlorophenyl)-2-(2,4-dimethylphenyl)-N-(3,5-dimethyl-4H-1,2,4-triazol-4-yl)-1H-imidazole-4-carboxamide | 424.2 | 0.26 (20% 2M NH ₃ /MeOH in EtOAc) | 2.37 | 1 | 13, 14 |
| 193 | 2,4-Cl ₂ -Ph | 4-F-Ph | Ph | 2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-N-phenyl-1H-imidazole-4-carboxamide | 426.1 | 0.46 (30% EtOAc in hexane) | 3.61 | 1 | 15 |

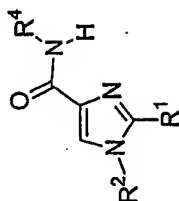
Table 8

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC R _f (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|--------------------------------|--|---------------------------|--|---------------|-------------|-----------------------------|
| 194 | 2-Cl-Ph | 4-Cl-Ph | 3-pyridinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(3-pyridinyl)-1H-imidazole-4-carboxamide | 409.3 | 0.25 (5% MeOH in EtOAc) | 2.44 | 1 | 15 |
| 195 | 2-Cl-Ph | 4-Cl-Ph | 2-pyridinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2-pyridinyl)-1H-imidazole-4-carboxamide | 409.1 | 0.25 (5% MeOH in CH ₂ Cl ₂) | 2.99 | 1 | 15 |
| 196 | 2-Cl-Ph | 4-Cl-Ph | 4-Cl-Ph | 2-(2-chlorophenyl)-N,1-bis(4-chlorophenyl)-1H-imidazole-4-carboxamide | 442.1 | 0.65 (30% EtOAc in hexane) | 3.79 | 1 | 15 |
| 197 | 2-Et-Ph | 4-Cl-Ph | Ph | 1-(4-chlorophenyl)-2-(2-ethylphenyl)-N-phenyl-1H-imidazole-4-carboxamide | 402.1 | 0.4 (50% EtOAc in hexane) | 3.71 | 1 | 13, 14 |
| 198 | 2-Cl-Ph | 4-Cl-Ph | 4-pyridinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-pyridinyl)-1H-imidazole-4-carboxamide | 409.5 | 0.37 (EtOAc) | 2.45 | 1 | 10, 11, 12 |
| 199 | 2-Cl-Ph | 4-Cl-Ph | 4-CF ₃ -3-pyridinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[4-(trifluoromethyl)-3-pyridinyl]-1H-imidazole-4-carboxamide | 477.3 | 0.44 (50% EtOAc in hexane) | 3.39 | 1 | 13, 14 |

Table 8

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC R _f (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|--------------------------------|--|---------------------------|------------------------------|---------------|-------------|-----------------------------|
| 200 | 2-Cl-Ph | 4-Cl-Ph | 4-Me-3-pyridinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-methyl-3-pyridinyl)-1H-imidazole-4-carboxamide | 423.3 | 0.31 (EtOAc) | 2.41 | 1 | 8 |
| 201 | 2-Cl-Ph | 4-Cl-Ph | 4-pyrimidinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-pyrimidinyl)-1H-imidazole-4-carboxamide hydrochloride | 410.4 | 0.27 (50% EtOAc in hexane) | 3.04 | 1 | 13, 14 |
| 202 | 2-Cl-Ph | 4-Cl-Ph | 2-pyrimidinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2-pyrimidinyl)-1H-imidazole-4-carboxamide | 410.6 | 0.32 (50% EtOAc in hexane) | 2.85 | 1 | 6 |
| 203 | 2-Cl-Ph | 4-Cl-Ph | 2-pyrazinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2-pyrazinyl)-1H-imidazole-4-carboxamide | 410.6 | 0.47 (75% EtOAc in hexane) | 3.18 | 1 | 6 |
| 204 | 2-Cl-Ph | 4-Cl-Ph | 5-CF ₃ -2-pyridinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[5-(trifluoromethyl)-2-pyridinyl]-1H-imidazole-4-carboxamide | 477.2 | 0.4 (25% EtOAc in hexane) | 3.77 | 1 | 6 |

Table 9



| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis method of Ex. No. |
|-----------|----------------|-------------------------|----------------------------|---|---------------------------|------------------|----------------|-------------|-----------------------------|
| 205 | 4-Cl-Ph | 2,4-Cl ₂ -Ph | 2-(1-piperidinyl)ethyl | 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-[2-(1-piperidinyl)ethyl]-1H-imidazole-4-carboxamide | 477 | | | | 13, 14 |
| 206 | 4-Cl-Ph | 2,4-Cl ₂ -Ph | 2-(Et ₂ N)ethyl | 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-[2-(diethylamino)ethyl]-1H-imidazole-4-carboxamide | 465 | | 2.54 | 1 | 13, 14 |
| 207 | 4-Cl-Ph | 2,4-Cl ₂ -Ph | 2-(Me ₂ N)ethyl | 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-[2-(dimethylamino)ethyl]-1H-imidazole-4-carboxamide | 437 | | 2.46 | 1 | 8 |

Table 9

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis method of Ex. No. |
|-----------|----------------|-------------------------|--------------------------------|--|---------------------------|----------------------------|----------------|-------------|-----------------------------|
| 208 | 4-Cl-Ph | 2,4-Cl ₂ -Ph | 3-(Me ₂ N)-1-propyl | 2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-[3-(dimethylamino)propyl]-1H-imidazole-4-carboxamide | 451 | | 2.48 | 1 | 13, 14 |
| 209 | 2-Cl-Ph | 4-Cl-Ph | endo-2-norbornyl | N-endo-bicyclo[2.2.1]hept-2-yl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide | 426 | 0.21 (40% EtOAc in hexane) | 3.50 | 1 | 15 |
| 210 | 2-Cl-Ph | 4-Cl-Ph | exo-2-norbornyl | N-exo-bicyclo[2.2.1]hept-2-yl-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide | 426 | 0.19 (30% EtOAc in hexane) | 3.49 | 1 | 15 |
| 211 | 2-Cl-Ph | 4-Cl-Ph | 1-propyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-propyl-1H-imidazole-4-carboxamide | 374 | 0.5 (30% EtOAc in hexane) | 3.10 | 1 | 15 |
| 212 | 2-Cl-Ph | 4-Cl-Ph | 3-pentyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1-ethylpropyl)-1H-imidazole-4-carboxamide | 402 | 0.21 (30% EtOAc in hexane) | 3.33 | 1 | 13, 14 |

Table 9

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis method of Ex. No. |
|-----------|----------------|----------------|---|---|---------------------------|----------------------------|----------------|-------------|-----------------------------|
| 213 | 2-Cl-Ph | 4-Cl-Ph | 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)-1H-imidazole-4-carboxamide | 468 | 0.29 (30% EtOAc in hexane) | 3.97 | 1 | 8 |
| 214 | 2-Cl-Ph | 4-Cl-Ph | trans-2-(HOCH ₂) ₂ -cyclohexyl | trans-2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[2-(hydroxymethyl)cyclohexyl]-1H-imidazole-4-carboxamide | 444 | 30% EtOAc/Hexane | 3.51 | 2 | 10, 11, 12 |
| 215 | 2-Cl-Ph | 4-Cl-Ph | 2,3-dihydro-1,4-benzodioxin-2-yl-CH ₂ | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1H-imidazole-4-carboxamide | 480 | | 3.88 | 2 | 10, 11, 12 |
| 216 | 2-Cl-Ph | 4-Cl-Ph | 2,4-Cl ₂ -benzyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2,4-dichlorobenzyl)-1H-imidazole-4-carboxamide | 490 | | 4.21 | 2 | 10, 11, 12 |
| 217 | 2-Cl-Ph | 4-Cl-Ph | 3-(1-pyrrolidinyl)-1-propyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[3-(1-pyrrolidinyl)propyl]-1H-imidazole-carboxamide hydrochloride | 443 | | 2.48 | 2 | 10, 11, 12 |

Table 9

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis method of Ex. No. |
|-----------|-------------------------|----------------|---|---|---------------------------|--|----------------|-------------|-----------------------------|
| 218 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | 3-(1-pyrrolidinyl)-1-propyl | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[3-(1-pyrrolidinyl)propyl]-1H-imidazole-4-carboxamide | 477 | 0.67 (40% 2M NH ₃ /MeOH in EtOAc) | 2.45 | 1 | 13, 14 |
| 219 | 2-CF ₃ -Ph | 4-Cl-Ph | 3-(1-pyrrolidinyl)-1-propyl | 1-(4-chlorophenyl)-N-[3-(1-pyrrolidinyl)propyl]-2-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carboxamide | 477 | | 2.55 | 2 | 10, 11, 12 |
| 220 | 2-Cl-Ph | 4-Cl-Ph | 1-benzyl-4-piperidinyl | N-(1-benzyl-4-piperidinyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide | 505 | | 2.66 | 2 | 10, 11, 12 |
| 221 | 2-Cl-Ph | 4-Cl-Ph | 1-CO ₂ Et-4-piperidinyl | ethyl 4-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)amino)-1-piperidinecarboxylate | 487 | 0.25 (83% EtOAc in hexane) | 3.01 | 1 | 13, 14 |
| 222 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | trans-2-(HOCH ₂) ₂ -cyclohexyl | trans-2-(2,4-dichlorophenyl)-N-[2-(hydroxymethyl)cyclohexyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 474 | | 3.58 | 2 | 10, 11, 12 |

Table 9

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis method of Ex. No. |
|-----------|-------------------------|----------------|---------------------------------------|---|---------------------------|---|----------------|-------------|-----------------------------|
| 223 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | 1-benzyl-4-piperidinyl | N-(1-benzyl-4-piperidinyl)-2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 535 | | 2.74 | 2 | 10, 11, 12 |
| 224 | 2-Cl-Ph | 4-Cl-Ph | 4-piperidinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-piperidinyl)-1H-imidazole-4-carboxamide | 415 | 0.25 (50% 2M NH ₃ /Me OH in EtOAc) | 2.22 | 1 | 37 |
| 225 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | cis-2-(HOCH ₂)-cyclohexyl | cis-2-(2,4-dichlorophenyl)-N-[2-(hydroxymethyl)cyclohexyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 474 | | 3.69 | 2 | 10, 11, 12 |
| 226 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | cis-2-OH-cycloheptyl-CH ₂ | cis-2-(2,4-dichlorophenyl)-N-[2-(hydroxycycloheptyl)methyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 488 | | 3.66 | 2 | 10, 11, 12 |
| 227 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | trans-2-OH-cyclohexyl-CH ₂ | trans-2-(2,4-dichlorophenyl)-N-[2-(hydroxycyclohexyl)methyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 474 | | 3.47 | 2 | 10, 11, 12 |

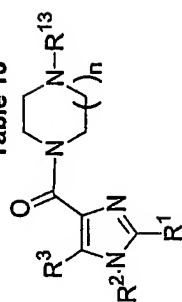
Table 9

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Syntheses method of Ex. No. |
|-----------|-------------------------|----------------|--|--|---------------------------|--|----------------|-------------|-----------------------------|
| 228 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | 3-exo-HOCH ₂ -2-exo-norbornyl | exo,exo-2-(2,4-dichlorophenyl)-N-[3-(hydroxymethyl)bicyclo[2.2.1]hept-2-yl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 486 | | 3.44 | 2 | 10, 11, 12 |
| 229 | 2-Cl-Ph | 4-Cl-Ph | 1-Me-4-piperidinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(1-methyl-4-piperidinyl)-1H-imidazole-4-carboxamide | 429 | 0.31(90% MeOH in 2M NH ₃ in MeOH) | 2.27 | 1 | 13, 14 |
| 230 | 2-Cl-Ph | 4-Cl-Ph | 1-(2-pyridinyl)-4-piperidinyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[1-(2-pyridinyl)-4-piperidinyl]-1H-imidazole-4-carboxamide | 492 | 0.33 (33% EtOAc in hexane) | 2.47 | 1 | 13, 14 |
| 231 | 2-Cl-Ph | 4-Cl-Ph | trans-2-(acetyloxy)-cyclohexyl | trans-2-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)amino)cyclohexyl acetate | 472 | 0.33 (50% EtOAc in hexane) | 3.25 | 1 | 13, 14 |
| 232 | 2-Cl-Ph | 4-Cl-Ph | 1-benzyl-3-pyrrolidinyl | N-(1-benzyl-3-pyrrolidinyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide hydrochloride | 491 | | 2.34 | 2 | 10, 11, 12 |

Table 9

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis method of Ex. No. |
|-----------|-------------------------|----------------|-------------------------------------|---|---------------------------|------------------|----------------|-------------|-----------------------------|
| 233 | 2-Cl-Ph | 4-Cl-Ph | 1-Et-2-pyrrolidinyl-CH ₂ | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-1H-imidazole-4-carboxamide hydrochloride | 443 | | 2.26 | 2 | 10, 11, 12 |
| 234 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | (R,R)-2-amino-cyclohexyl | N-[(1R,2R)-2-aminocyclohexyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide hydrochloride | 463 | | 2.37 | 2 | 10, 11, 12 |
| 235 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | (S,S)-2-amino-cyclohexyl | N-[(1S,2S)-2-aminocyclohexyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide hydrochloride | 463 | | 2.34 | 2 | 10, 11, 12 |

Table 10



| Entry No. | R ¹ | R ² | R ³ | n | R ¹³ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|---|-------------------------|---|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 236 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | 2,3-Me ₂ -Ph | 1-[[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2,3-dimethylphenyl)piperazine | 539 | 0.55 (50% EtOAc in hexane) | 4.17 | 1 | 13, 14 |
| 237 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | 2,4-F ₂ -Ph | 1-[[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2,4-difluorophenyl)piperazine | 549 | 0.27 (60% EtOAc in hexane) | 3.71 | 1 | 13, 14 |
| 238 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | 2-CN-Ph | 2-(4-[[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl]-1-piperazinyl)benzonitrile | 536 | 0.73 (EtOAc) | 3.69 | 1 | 13, 14 |

Table 10

| Entry No. | R ¹ | R ² | R ³ | n | R ¹³ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|---|-----------------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 239 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | 2-phenylethyl | 1-[[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2-phenylethyl)piperazine | 539 | 0.30 (2% MeOH in EtOAc) | 2.79 | 1 | 13, 14 |
| 240 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | 2-pyridinyl | 1-[[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2-pyridinyl)piperazine | 512 | 0.6 (EtOAc) | 2.48 | 1 | 10, 11, 12 |
| 241 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | 3-CF ₃ -Ph | 1-[[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-[3-(trifluoromethyl)phenyl]piperazine | 579 | 0.44 (50% EtOAc in hexane) | 4.11 | 1 | 13, 14 |
| 242 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | 3-MeO-Ph | 1-[[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(3-methoxyphenyl)piperazine | 541 | 0.31 (60% EtOAc in hexane) | 3.62 | 1 | 13, 14 |
| 243 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | 4-Cl-Ph | 1-(4-chlorophenyl)-4-[[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl]piperazine | 545 | 0.72 (EtOAc) | 4.13 | 1 | 13, 14 |

Table 10

| Entry No. | R ¹ | R ² | R ³ | n | R ¹³ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|---|-----------------------|---|---------------------------|---------------------------|---------------|-------------|-----------------------------|
| 244 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | 4-CN-Ph | 4-(4-([1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl)-1-piperazinyl)benzonitrile | 536 | 0.3 (66% EtOAc in hexane) | 3.61 | 1 | 13, 14 |
| 245 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | benzyl | 1-benzyl-4-([1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl)piperazine | 525 | 0.30 (EtOAc) | 2.62 | 1 | 13, 14 |
| 246 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | cyclohexyl | 1-([1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl)-4-cyclohexylpiperazine hydrochloride | 519 | 0.07 (EtOAc) | 2.61 | 1 | 13, 14 |
| 247 | 2,4-Cl ₂ -Ph | 4-F-Ph | H | 1 | 4-CF ₃ -Ph | 1-([2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazol-4-yl]carbonyl)-4-[4-(trifluoromethyl)phenyl]piperazine trifluoroacetate | 563 | | 3.73 | 2 | 10, 11, 12 |
| 248 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | 1 | 2-HO-Ph | 2-(4-([2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl)-1-piperazinyl)phenol hydrochloride | 523 | | 2.81 | 2 | 10, 11, 12 |

Table 10

| Entry No. | R ¹ | R ² | R ³ | n | R ¹³ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|---|-----------------------|---|---------------------------|------------------|---------------|-------------|-----------------------------|
| 249 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | 1 | 2-pyrazinyl | 2-(4-([2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl)-1-piperazinyl)pyrazine bis(trifluoroacetate) | 509 | | 2.59 | 2 | 10, 11, 12 |
| 250 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | 1 | 3-CF ₃ -Ph | 1-([2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl)-4-[3-(trifluoromethyl)phenyl]piperazine hydrochloride | 575 | | 4.24 | 2 | 10, 11, 12 |
| 251 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | 1 | 6-Me-2-pyridinyl | 1-([2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl)-4-(6-methyl-2-pyridinyl)piperazine hydrochloride | 522 | | 2.19 | 2 | 10, 11, 12 |
| 252 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | 1 | 4-CF ₃ -Ph | 1-([2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl)-4-[4-(trifluoromethyl)phenyl]piperazine | 574 | | 4.34 | 2 | 10, 11, 12 |
| 253 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | 1 | 4-CF ₃ -Ph | 1-([2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl)-4-[4-(trifluoromethyl)phenyl]piperazine hydrochloride | 574 | | 4.34 | 2 | 10, 11, 12 |

Table 10

| Entry No. | R ¹ | R ² | R ³ | n | R ¹³ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|---|-----------------------|---|---------------------------|------------------|---------------|-------------|-----------------------------|
| 254 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | 1 | 4-HO-Ph | 4-(4-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)phenol hydrochloride | 523 | | 2.52 | 2 | 10, 11, 12 |
| 255 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | 1 | 4-pyridinyl | 1-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-pyridinyl)piperazine hydrochloride | 508 | | 2.56 | 2 | 10, 11, 12 |
| 256 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | 1 | 4-pyridinyl-methyl | 1-{[2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-pyridinylmethyl)piperazine dihydrochloride | 522 | | 2.04 | 2 | 10, 11, 12 |
| 257 | 2,5-Cl ₂ -Ph | 4-Cl-Ph | H | 1 | 4-CN-Ph | 4-(4-{[1-(4-chlorophenyl)-2-(2,5-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile | 536 | | 3.69 | 1 | 8 |
| 258 | 2-CF ₃ -Ph | 4-Cl-Ph | H | 1 | 3-CF ₃ -Ph | 1-{[1-(4-chlorophenyl)-2-[2-(trifluoromethyl)phenyl]-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluoromethyl)phenyl]piperazine hydrochloride | 579 | | 4.25 | 2 | 10, 11, 12 |

Table 10

| Entry No. | R ¹ | R ² | R ³ | n | R ¹³ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|---|------------------------|---|---------------------------|------------------|---------------|-------------|-----------------------------|
| 259 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | 2,4-F ₂ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2,4-difluorophenyl)piperazine hydrochloride | 513 | | 3.4 | 2 | 10, 11, 12 |
| 260 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | 2-CN-Ph | 2-(4-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-1-piperazinyl)benzonitrile hydrochloride | 502 | | 3.25 | 2 | 10, 11, 12 |
| 261 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | 2-HO-Ph | 2-(4-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-1-piperazinyl)phenol hydrochloride | 493 | | 2.78 | 2 | 10, 11, 12 |
| 262 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | 2-hydroxyethyl | 2-(4-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-1-piperazinyl)ethanol hydrochloride | 445 | | 2.42 | 2 | 10, 11, 12 |
| 263 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | 2-pyridinyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2-pyridinyl)piperazine dihydrochloride | 478 | | 2.63 | 2 | 10, 11, 12 |

Table 10

| Entry No. | R ¹ | R ² | R ³ | n | R ¹³ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|---|-----------------------|--|---------------------------|------------------|---------------|-------------|-----------------------------|
| 264 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | 3-CF ₃ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-[3-(trifluoromethyl)phenyl]piperazine hydrochloride | 545 | | 4.24 | 2 | 10, 11, 12 |
| 265 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | 3-Cl-Ph | 1-(3-chlorophenyl)-4-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]piperazine hydrochloride | 511 | | 4.13 | 2 | 10, 11, 12 |
| 266 | 2-Cl-Ph | 4-Cl-Ph | cyclo-Pr | 1 | 4-CF ₃ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-cyclopropyl-1H-imidazol-4-yl]carbonyl]-4-[4-(trifluoromethyl)phenyl]piperazine hydrochloride | 585 | | 3.7 | 2 | 13, 14 |
| 267 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | 4-CF ₃ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-[4-(trifluoromethyl)phenyl]piperazine hydrochloride | 545 | | 4.21 | 2 | 10, 11, 12 |
| 268 | 2-Cl-Ph | 4-Cl-Ph | cyclo-Pr | 1 | 4-CN-Ph | 4-(4-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-cyclopropyl-1H-imidazol-4-yl]carbonyl]-1-piperazinyl)benzonitrile hydrochloride | 542 | | 3.29 | 2 | 13, 14 |

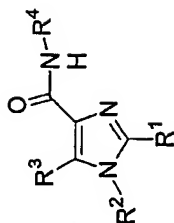
Table 10

| Entry No. | R ¹ | R ² | R ³ | n | R ¹³ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|---|-----------------|---|---------------------------|------------------|---------------|-------------|-----------------------------|
| 269 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | 4-CN-Ph | 4-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile | 502 | | 3.18 | 2 | 10, 11, 12 |
| 270 | 2-Cl-Ph | 4-Cl-Ph | H | 2 | 4-F-benzyl | 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-fluorobenzyl)-1,4-diazepane hydrochloride | 523 | | 2.68 | 2 | 10, 11, 12 |
| 271 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | 4-F-benzyl | 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-fluorobenzyl)piperazine hydrochloride | 509 | | 2.67 | 2 | 10, 11, 12 |
| 272 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | 4-HO-Ph | 4-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)phenol hydrochloride | 493 | | 2.44 | 2 | 10, 11, 12 |
| 273 | 2-Cl-Ph | 4-Cl-Ph | H | 1 | cyclohexyl | 1-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-cyclohexylpiperazine hydrochloride | 483 | | 2.63 | 2 | 10, 11, 12 |

Table 10

| Entry No. | R ¹ | R ² | R ³ | n | R ¹³ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|-----------------------|----------------|---|-----------------------|--|---------------------------|----------------------------|---------------|-------------|-----------------------------|
| 274 | 2-Cl-Ph | 4-Me-Ph | H | 1 | 2-hydroxyethyl | 2-(4-[(2-(2-chlorophenyl))-1-(4-methylphenyl)-1H-imidazol-4-yl]carbonyl)-1-piperazinyl)ethanol hydrochloride | 425 | | 2.34 | 2 | 10, 11, 12 |
| 275 | 2-Cl-Ph | 4-NO ₂ -Ph | Me | 1 | 3-CF ₃ -Ph | 1-[(2-(2-chlorophenyl)-5-methyl-1-(4-nitrophenyl)-1H-imidazol-4-yl]carbonyl)-4-[3-(trifluoromethyl)phenyl]piperazine | 570 | 0.35 (67% EtOAc in hexane) | 3.64 | 1 | 8 |

Table 11



| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|-----------------------------------|--|---------------------------|----------------------------|----------------------|-------------|-----------------------------|
| 276 | 2-Cl-Ph | 4-Cl-Ph | H | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide | 520.3 | 0.35 (60% EtOAc in Hexane) | 3.69 | 1 | 13, 14 |
| 277 | 2-Cl-Ph | 4-Cl-Ph | H | (1R,2R)-2-(benzyloxy)-cyclopentyl | N-[(1R,2R)-2-(benzyloxy)cyclopentyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide | 506.3 | 0.56 (50% EtOAc in Hexane) | 3.51 | 1 | 13, 14 |
| 278 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | (1R,2R)-2-(benzyloxy)-cyclohexyl | N-[(1R,2R)-2-(benzyloxy)cyclohexyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide | 554.4 | 0.46 (50% EtOAc in Hexane) | 3.99 | 1 | 13, 14 |
| 279 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide | 554.4 | 0.46 (50% EtOAc in Hexane) | 4.00 | 1 | 13, 14 |

Table 11

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|-----------------------------------|--|---------------------------|----------------------------|----------------------|-------------|-----------------------------|
| 280 | 2-Cl-Ph | 4-Cl-Ph | H | (1R,2R)-2-(benzyloxy)-cyclohexyl | N-[(1R,2R)-2-(benzyloxy)cyclohexyl]-1-(4-chlorophenyl)-2-(2-chlorophenyl)-1H-imidazole-4-carboxamide | 520.3 | 0.33 (66% EtOAc in Hexane) | 3.67 | 1 | 13,14 |
| 281 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | (1R,2R)-2-(benzyloxy)-cyclopentyl | N-[(1R,2R)-2-(benzyloxy)cyclopentyl]-2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide | 540.0 | 0.41 (40% EtOAc in Hexane) | 4.07 | 1 | 13,14 |
| 282 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | (1S,2S)-2-(benzyloxy)-cyclopentyl | N-[(1S,2S)-2-(benzyloxy)cyclopentyl]-2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide | 540.0 | 0.41 (40% EtOAc in Hexane) | 4.07 | 1 | 13,14 |
| 283 | 2-Cl-Ph | 4-Cl-Ph | H | (1S,2S)-2-(benzyloxy)-cyclopentyl | N-[(1S,2S)-2-(benzyloxy)cyclopentyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide | 506.1 | 0.32 (40% EtOAc in Hexane) | 3.78 | 1 | 13,14 |
| 284 | 2-Cl-Ph | 4-Cl-Ph | Et | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazole-4-carboxamide | 548.6 | 0.33 (33% EtOAc in Hexane) | 3.81 | 1 | 13,14 |

Table 11

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|--|---|---------------------------|----------------------------|----------------------|-------------|-----------------------------|
| 285 | 2-Cl-Ph | 4-Cl-Ph | Pr | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazole-4-carboxamide | 562.2 | 0.20 (25% EtOAc in Hexane) | 4.18 | 1 | 13,14 |
| 286 | 2-Cl-Ph | 4-Cl-Ph | H | trans-2-(ethoxycarbonylmethoxy)-cyclohexyl | ethyl {[trans-2-({[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}amino)cyclohexyl]oxy}acetate | 516.2 | 0.37 (67% EtOAc in Hexane) | 3.37 | 1 | 13,14 |
| 287 | 2-Cl-Ph | 4-Cl-Ph | H | trans-2-(2'-hydroxyethoxy)-cyclohexyl | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[trans-2-(2-hydroxyethoxy)cyclohexyl]-1H-imidazole-4-carboxamide | 474.8 | 0.17 (EtOAc) | 2.91 | 1 | 13,14 |
| 288 | 2-Cl-Ph | 4-Br-Ph | Et | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-1H-imidazole-4-carboxamide | 592.9 | 0.29 (33% EtOAc in Hexane) | 4.31 | 1 | 13,14 |
| 289 | 2-Cl-Ph | 4-iPr-Ph | Et | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-1-(4-isopropylphenyl)-2-(2-chlorophenyl)-5-ethyl-1H-imidazole-4-carboxamide | 556.3 | 0.79 (2:1 EtOAc/Hexane) | 4.09 | 1 | 13,14 |

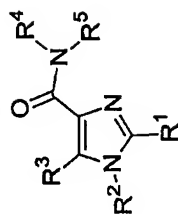
Table 11

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------------------------|--|---------------------------|-------------------------|----------------------|-------------|-----------------------------|
| 290 | 2-Cl-Ph | 4-Cl-Ph | Br | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide | 598 | | 3.80 | 2 | 13,14 |
| 291 | 2-Cl-Ph | 4-MeO-Ph | Pr | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-methoxyphenyl)-5-propyl-1H-imidazole-4-carboxamide | 558.3 | 0.60 (1:1 EtOAc/Hexane) | 3.86 | 1 | 13,14 |
| 292 | 2-Cl-Ph | 4-F-Ph | Pr | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-fluorophenyl)-5-propyl-1H-imidazole-4-carboxamide | 546.3 | 0.19 (1:1 EtOAc/Hexane) | 3.90 | 1 | 13,14 |
| 293 | 2-Cl-Ph | 3-Cl-Ph | Pr | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(3-chlorophenyl)-5-propyl-1H-imidazole-4-carboxamide | 562.3 | 0.73 (1:1 EtOAc/Hexane) | 4.07 | 1 | 13,14 |
| 294 | 2-Cl-Ph | 2-Cl-4-F-Ph | H | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(2-chloro-4-fluorophenyl)-1H-imidazole-4-carboxamide | 538.2 | 0.44 (1:1 EtOAc/Hexane) | 3.64 | 1 | 13,14 |

Table 11

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|------------------------|----------------|----------------------------------|---|---------------------------|-------------------------|----------------------|-------------|-----------------------------|
| 295 | 2-Cl-Ph | 2,4-F ₂ -Ph | H | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(2,4-difluorophenyl)-1H-imidazole-4-carboxamide | 522.2 | 0.29 (1:1 EtOAc/Hexane) | 3.56 | 1 | 13,14 |
| 296 | 2-Cl-Ph | 4-CF ₃ -Ph | Pr | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-trifluoromethoxyphenyl)-5-propyl-1H-imidazole-4-carboxamide | 612.3 | 0.41 (1:1 EtOAc/Hexane) | 4.17 | 1 | 13,14 |
| 297 | 2-Cl-Ph | 4-Cl-Ph | i-Pr | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-isopropyl-1H-imidazole-4-carboxamide | 562 | | 3.98 | 2 | 13,14 |
| 298 | 2-Cl-Ph | 4-Cl-Ph | cyclo-Pr | (1S,2S)-2-(benzyloxy)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-cyclopropyl-1H-imidazole-4-carboxamide | 560.3 | | 3.72 | 2 | 13,14 |

Table 12



| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|--------------------|----------------|----------------|----------------|---|---------------------------|-------------------------|----------------------|-------------|-----------------------------|
| 299 | 2-Cl-Ph | 4- <i>i</i> -Pr-Ph | Et | H | | 2-(2-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1-(4-isopropylphenyl)-1H-imidazole-4-carboxamide | 466 | 0.49 (2:1 EtOAc/Hexane) | 3.38 | 1 | 13,14 |
| 300 | 2-Cl-Ph | 4-MeO-Ph | <i>n</i> -Pr | H | | 2-(2-chlorophenyl)-5-propyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 468 | 0.66 (EtOAc) | 3.09 | 1 | 13,14 |
| 301 | 2-Cl-Ph | 4-F-Ph | <i>n</i> -Pr | H | | 2-(2-chlorophenyl)-5-propyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1-(4-fluorophenyl)-1H-imidazole-4-carboxamide | 456 | 0.35 (2:1 EtOAc/Hexane) | 3.16 | 1 | 13,14 |

Table 12




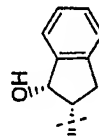
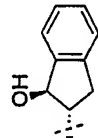
| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|------------------------|----------------|----------------|---|--|---------------------------|-------------------------|----------------------|-------------|-----------------------------|
| 302 | 2-Cl-Ph | 3-Cl-Ph | n-Pr | H |  | 2-(2-chlorophenyl)-5-propyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1-(3-chlorophenyl)-1H-imidazole-4-carboxamide | 472 | 0.45 (2:1 EtOAc/Hexane) | 3.29 | 1 | 13,14 |
| 303 | 2-Cl-Ph | 2-Cl-4-F-Ph | H | H |  | 1-(2-chloro-4-fluorophenyl)-2-(2-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 448 | 0.5 (EtOAc) | 2.90 | 1 | 13,14 |
| 304 | 2-Cl-Ph | 2,4-F ₂ -Ph | H | H |  | 2-(2-chlorophenyl)-1-(2,4-difluorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 432 | 0.5 (EtOAc) | 2.82 | 1 | 13,14 |
| 305 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[cis-1-hydroxy-2,3-dihydro-1H-inden-2-yl]-1H-imidazole-4-carboxamide | 464 | | 3.16 | 1 | 13,14 |
| 306 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[trans-1-hydroxy-2,3-dihydro-1H-inden-2-yl]-1H-imidazole-4-carboxamide | 464 | | 3.15 | 1 | 13,14 |

Table 12

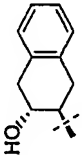
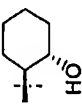
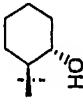
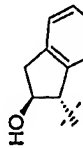
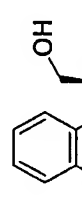
| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|--|---|--|---------------------------|-------------------------|----------------------|-------------|-----------------------------|
| 307 | 2-Cl-Ph | 4-Cl-Ph | H | 2,4-(MeO) ₂ -Ph-CH ₂ - |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(2,4-dimethoxybenzyl)-N-[trans-3-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl]-1H-imidazole-4-carboxamide | 529 | 0.15 (1:1 EtOAc/Hexane) | 3.72 | 1 | 13,14 |
| 308 | 2-Cl-Ph | 4-Cl-Ph | Br | H |  | 5-bromo-2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 508 | | 2.99 | 2 | 13,14 |
| 309 | 2-Cl-Ph | 4-Cl-Ph | <i>i</i> -Pr | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-5-isopropyl-1H-imidazole-4-carboxamide | 472 | | 3.22 | 2 | 13,14 |
| 310 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[trans-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-1H-imidazole-4-carboxamide | 464 | | 3.05 | 2 | 10,11,12 |
| 311 | 2-Cl-Ph | 4-Cl-Ph | H | |  | ((3S)-2-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-1,2,3,4-tetrahydro-3-isoquinolyl)methanol | 478 | | 3.00 | 2 | 10,11,12 |

Table 12

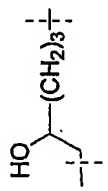
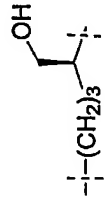
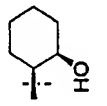
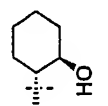
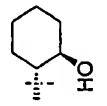
| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------|---|---|---------------------------|---------------|----------------------|-------------|-----------------------------|
| 312 | 2-Cl-Ph | 4-Cl-Ph | H | |  | 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-3-piperidinol | 416 | | 2.56 | 2 | 10,11,12 |
| 313 | 2-Cl-Ph | 4-Cl-Ph | H | |  | ((2S)-1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-2-pyrrolidinyl)methanol | 416 | | 2.59 | 2 | 10,11,12 |
| 314 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | H |  | 2-(2,4-dichlorophenyl)-N-[cis-2-hydroxycyclohexyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 460 | | 3.69 | 2 | 10,11,12 |
| 315 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | H |  | 2-(2,4-dichlorophenyl)-N-[trans-2-hydroxycyclohexyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 460 | | 3.40 | 2 | 10,11,12 |
| 316 | 2-Me-Ph | 4-Cl-Ph | H | H |  | 1-(4-chlorophenyl)-N-[trans-2-(2-methoxycyclohexyl)-2-(2-methylphenyl)-1H-imidazol-4-yl]carboxamide | 411 | | 2.74 | 2 | 10,11,12 |

Table 12

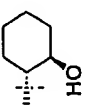
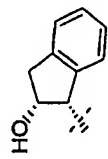
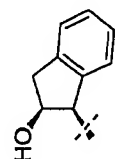
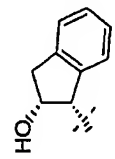
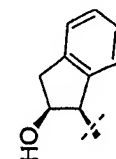
| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------|---|--|---------------------------|---------------|----------------------|-------------|-----------------------------|
| 317 | 2,4-Cl ₂ -Ph | 4-F-Ph | H | H |  | 1-(4-fluorophenyl)-N-[trans-2-hydroxycyclohexyl]-2-(2,4-dichlorophenyl)-1H-imidazole-4-carboxamide | 449 | | 2.85 | 2 | 10,11,12 |
| 318 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | H |  | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-1H-imidazole-4-carboxamide | 498 | | 3.29 | 2 | 10,11,12 |
| 319 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | H |  | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-1H-imidazole-4-carboxamide | 498 | | 3.29 | 2 | 10,11,12 |
| 320 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-1H-imidazole-4-carboxamide | 464 | | 3.11 | 2 | 10,11,12 |
| 321 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-1H-imidazole-4-carboxamide | 464 | | 3.11 | 2 | 10,11,12 |

Table 12


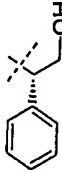

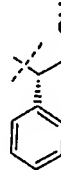

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------|---|--|---------------------------|---------------|----------------------|-------------|-----------------------------|
| 322 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | H |  | 2-(2,4-dichlorophenyl)-N-[(1R)-2-hydroxy-1-phenylethyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 483 | | 2.99 | 2 | 10,11,12 |
| 323 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | H |  | 2-(2,4-dichlorophenyl)-N-[(1S)-2-hydroxy-1-phenylethyl]-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamide | 483 | | 2.96 | 2 | 10,11,12 |
| 324 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-N-[(1R)-2-hydroxy-1-phenylethyl]-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide | 452 | | 2.88 | 2 | 10,11,12 |
| 325 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-N-[(1S)-2-hydroxy-1-phenylethyl]-1-(4-chlorophenyl)-1H-imidazole-4-carboxamide | 453 | | 2.89 | 2 | 10,11,12 |
| 326 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[1-(hydroxymethyl)cyclopentyl]-1H-imidazole-4-carboxamide | 431 | | 2.89 | 2 | 10,11,12 |

Table 12

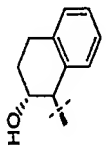

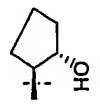
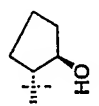
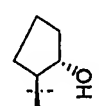
| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------|---|--|---------------------------|----------------------------|----------------------|-------------|-----------------------------|
| 327 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(trans-2-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl)-1H-imidazole-4-carboxamide | 477 | | 2.92 | 2 | 10,11,12 |
| 328 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | H |  | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(trans-2-hydroxycyclohexyl)-1H-imidazole-4-carboxamide | 464 | 0.14 (50% EtOAc in Hexane) | 3.20 | 1 | 13,14 |
| 329 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide | 416 | 0.43 (50% EtOAc in Hexane) | 2.96 | 1 | 36 |
| 330 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | H |  | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1R,2R)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide | 450 | 0.45 (50% EtOAc in Hexane) | 3.24 | 1 | 36 |
| 331 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | H |  | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1S,2S)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide | 450 | 0.45 (50% EtOAc in Hexane) | 3.24 | 1 | 36 |

Table 12




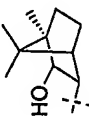

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|----------------|---|---|---------------------------|--|----------------------|-------------|-----------------------------|
| 332 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | H |  | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 464 | 0.67 (EtOAc) | 3.22 | 1 | 35 |
| 333 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1R,2R)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide | 416 | 0.4 (EtOAc) | 2.83 | 1 | 36 |
| 334 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | H |  | 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 466 | 0.67 (EtOAc) | 3.32 | 1 | 35 |
| 335 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2R,3S,4R)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1H-imidazole-4-carboxamide | 484 | 0.22 (50% EtOAc in Hexane) | 3.55 | 1 | 8 |
| 336 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[trans-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 430 | 0.45 (5% MeOH in CH ₂ Cl ₂) | 2.95 | 1 | 13,14 |

Table 12






| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------|---|---|---------------------------|----------------------------|----------------------|-------------|-----------------------------|
| 337 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[cis-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 430 | 0.31 (66% EtOAc in Hexane) | 2.94 | 1 | 13, 14 |
| 338 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 430 | 0.30 (66% EtOAc in Hexane) | 3.02 | 1 | 35 |
| 339 | 2-Cl-Ph | 4-Cl-Ph | H | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1R,2R)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 430 | 0.30 (66% EtOAc in Hexane) | 2.96 | 1 | 35 |
| 340 | 2-Cl-Ph | 4-Cl-Ph | Et | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 458 | 0.37 (75% EtOAc in Hexane) | 3.24 | 1 | 35 |
| 341 | 2-Cl-Ph | 4-Cl-Ph | n-Pr | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 472 | 0.41 (75% EtOAc in Hexane) | 3.38 | 1 | 35 |

Table 12

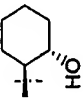
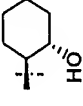
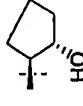
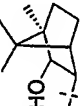

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------|---|--|---------------------------|----------------------------|----------------------|-------------|-----------------------------|
| 342 | 2-Cl-Ph | 4-Br-Ph | Et | H |  | 2-(2-chlorophenyl)-1-(4-bromophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 502 | 0.45 (EtOAc) | 3.19 | 1 | 35 |
| 343 | 2-Cl-Ph | 4-Cl-Ph | Me | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-methyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 444 | 0.29 (80% EtOAc in Hexane) | 3.06 | 1 | 35 |
| 344 | 2-Cl-Ph | 4-Cl-Ph | Et | H |  | 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide | 444 | 0.30 (67% EtOAc in Hexane) | 3.15 | 1 | 36 |
| 345 | 2-Cl-Ph | 4-Br-Ph | Et | H |  | 2-(2-chlorophenyl)-1-(4-bromophenyl)-N-[(1S,2R,3S,4R)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-5-ethyl-1H-imidazole-4-carboxamide | 556 | 0.40 (50% EtOAc in Hexane) | 3.97 | 1 | 8 |
| 346 | 2-Cl-Ph | 4-Br-Ph | Et | H |  | 2-(2-chlorophenyl)-1-(4-bromophenyl)-N-[(1R,2S,3R,4S)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-5-ethyl-1H-imidazole-4-carboxamide | 556 | 0.40 (50% EtOAc in Hexane) | 4.00 | 1 | 8 |

Table 12

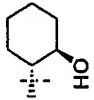
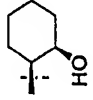
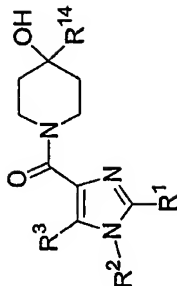
| Entry No. | R ¹ | R ² | R ³ | R ⁴ | R ⁵ | IUPAC name | MS m/z [MH ⁺] | TLC (solvent) | HPLC ret. time (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------|---|---|---------------------------|----------------------------|----------------------|-------------|-----------------------------|
| 347 | 2-Cl-Ph | 4-Br-Ph | Et | H |  | 1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(1R,2R)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 502 | 0.45 (EtOAc) | 3.31 | 1 | 35 |
| 348 | 2-Cl-Ph | 4-Br-Ph | Et | H |  | 1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[cis-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 502 | 0.26 (50% EtOAc in hexane) | 502.3 | 1 | 23 |

Table 13



| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|-------------------------------|--|---------------|-------------------------|---------------|-------------|-----------------------------|
| 349 | 2-Cl-Ph | 4-Cl-Ph | H | 1,1-dioxido-1-benzothien-2-yl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(1,1-dioxido-1-benzothien-2-yl)-4-piperidinol | 580 | 0.29 (EtOAc) | 3.10 | 1 | 18 |
| 350 | 2-Cl-Ph | 4-Cl-Ph | H | 1,3-thiazol-2-yl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(1,3-thiazol-2-yl)-4-piperidinol | 499 | 0.10 (1:2 Hexane/EtOAc) | 2.83 | 1 | 18 |
| 351 | 2-Cl-Ph | 4-Cl-Ph | H | 1-benzofuran-2-yl | 4-(1-benzofuran-2-yl)-1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-piperidinol | 532 | 0.45 (EtOAc) | 3.44 | 1 | 18 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|-------------------|---|---------------|------------------|---------------|-------------|-----------------------------|
| 352 | 2-Cl-Ph | 4-Cl-Ph | Et | 1-benzofuran-2-yl | 4-((1-benzofuran-2-yl)-1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl))-4-piperidinol | 560 | 0.39 (EtOAc) | 3.43 | 1 | 18 |
| 353 | 2-Cl-Ph | 4-Cl-Ph | nPr | 1-benzofuran-2-yl | 4-((1-benzofuran-2-yl)-1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl))-4-piperidinol | 574 | 0.40 (EtOAc) | 3.55 | 1 | 18 |
| 354 | 2-Cl-Ph | 4-Cl-Ph | H | 1-benzothien-2-yl | 4-((1-benzothien-2-yl)-1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl))-4-piperidinol | 548 | 0.50 (EtOAc) | 3.45 | 1 | 18 |
| 355 | 2-Cl-Ph | 4-Cl-Ph | nPr | 1-benzothien-2-yl | 4-((1-benzothien-2-yl)-1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl))-4-piperidinol | 590 | 0.45 (EtOAc) | 3.66 | 1 | 18 |
| 356 | 2-Cl-Ph | 4-Cl-Ph | Et | 1-benzothien-2-yl | 4-((1-benzothien-2-yl)-1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl))-4-piperidinol | 576 | 0.44 (EtOAc) | 3.54 | 1 | 18 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------------------------|---|---------------|-------------------------|---------------|-------------|-----------------------------|
| 357 | 2-Cl-Ph | 4-Cl-Ph | H | 2,3-dihydro-1,4-benzodioxin-6-yl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-piperidinol | 550 | 0.20 (1:2 Hexane/EtOAc) | 3.02 | 1 | 18 |
| 358 | 2-Cl-Ph | 4-Cl-Ph | H | 2,6-dimethyl-3-pyridinyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2,6-dimethyl-3-pyridinyl)-4-piperidinol | 521 | 0.04 (EtOAc) | 2.24 | 1 | 18 |
| 359 | 2-Cl-Ph | 4-Cl-Ph | H | 2,4-(MeO) ₂ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2,4-dimethoxyphenyl)-4-piperidinol | 552 | 0.16 (1:2 Hexane/EtOAc) | 3.20 | 1 | 18 |
| 360 | 2-Cl-Ph | 4-Cl-Ph | H | 2,5-F ₂ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2,5-difluorophenyl)-4-piperidinol | 528 | 0.24 (1:2 Hexane/EtOAc) | 3.28 | 1 | 18 |
| 361 | 2-Cl-Ph | 4-Cl-Ph | H | 2,5-(MeO) ₂ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2,5-dimethoxyphenyl)-4-piperidinol | 552 | 0.23 (1:2 Hexane/EtOAc) | 3.15 | 1 | 18 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|------------------------|---|---------------|-------------------------|---------------|-------------|-----------------------------|
| 362 | 2-Cl-Ph | 4-Cl-Ph | H | 2-CF ₃ O-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-[2-(trifluoromethoxy)phenyl]-4-piperidinol | 576 | 0.22 (1:2 Hexane/EtOAc) | 3.45 | 1 | 18 |
| 363 | 2-Cl-Ph | 4-Cl-Ph | H | 2-CF ₃ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-[2-(trifluoromethyl)phenyl]-4-piperidinol | 560 | 0.24 (1:2 Hexane/EtOAc) | 3.41 | 1 | 18 |
| 364 | 2-Cl-Ph | 4-Cl-Ph | H | 2-Cl-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2-chlorophenyl)-4-piperidinol | 526 | 0.13 (1:2 Hexane/EtOAc) | 3.34 | 1 | 18 |
| 365 | 2-Cl-Ph | 4-Cl-Ph | H | 2-F-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2-fluorophenyl)-4-piperidinol | 510 | 0.13 (1:2 Hexane/EtOAc) | 3.24 | 1 | 18 |
| 366 | 2-Cl-Ph | 4-Cl-Ph | H | 2-furyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2-furyl)-4-piperidinol | 482 | 0.22 (1:2 Hexane/EtOAc) | 2.98 | 1 | 18 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|-----------------|---|---------------|-------------------------|---------------|-------------|-----------------------------|
| 367 | 2-Cl-Ph | 4-Cl-Ph | Et | 2-furyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl]-4-(2-furyl)-4-piperidinol | 510 | 0.29 (1:2 Hexane/EtOAc) | 3.04 | 1 | 18 |
| 368 | 2-Cl-Ph | 4-Cl-Ph | H | 2-MeO-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2-methoxyphenyl)-4-piperidinol | 522 | 0.22 (1:2 Hexane/EtOAc) | 3.23 | 1 | 18 |
| 369 | 2-Cl-Ph | 4-Cl-Ph | H | 2-pyridinyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2-pyridinyl)-4-piperidinol | 493 | 0.05 (1:2 Hexane/EtOAc) | 2.26 | 1 | 18 |
| 370 | 2-Cl-Ph | 4-Cl-Ph | H | 2-thienyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(2-thienyl)-4-piperidinol | 498 | 0.22 (1:2 Hexane/EtOAc) | 3.11 | 1 | 18 |
| 371 | 2-Cl-Ph | 4-Cl-Ph | nPr | 2-thienyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl]-4-(2-thienyl)-4-piperidinol | 540 | 0.41 (EtOAc) | 3.33 | 1 | 18 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------------------|--|---------------|-------------------------|---------------|-------------|-----------------------------|
| 372 | 2-Cl-Ph | 4-Cl-Ph | Et | 2-thienyl | 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl)-4-(2-thienyl)-4-piperidinol | 526 | 0.42 (EtOAc) | 3.20 | 1 | 18 |
| 373 | 2-Cl-Ph | 4-Cl-Ph | Et | 3-CF ₃ -4-Cl-Ph | 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl)-4-[4-chloro-3-(trifluoromethyl)phenyl]-4-piperidinol | 622 | 0.47 (EtOAc) | 3.73 | 1 | 18 |
| 374 | 2-Cl-Ph | 4-Cl-Ph | nPr | 3-CF ₃ -4-Cl-Ph | 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl)-4-[4-chloro-3-(trifluoromethyl)phenyl]-4-piperidinol | 636 | 0.42 (EtOAc) | 3.82 | 1 | 18 |
| 375 | 2-Cl-Ph | 4-Cl-Ph | H | 3-CF ₃ O-Ph | 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-4-[3-(trifluoromethoxy)phenyl]-4-piperidinol | 576 | 0.38 (1:2 Hexane/EtOAc) | 3.37 | 1 | 18 |
| 376 | 2-Cl-Ph | 4-Cl-Ph | Et | 3-CF ₃ -Ph | 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl)-4-[3-(trifluoromethyl)phenyl]-4-piperidinol | 588 | 0.46 (EtOAc) | 3.55 | 1 | 18 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|---------------------------|---|---------------|-------------------------|---------------|-------------|-----------------------------|
| 377 | 2-Cl-Ph | 4-Cl-Ph | nPr | 3-CF ₃ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl]-4-[3-(trifluoromethyl)phenyl]-4-piperidinol | 602 | 0.43 (EtOAc) | 3.65 | 1 | 18 |
| 378 | 2-Cl-Ph | 4-Cl-Ph | H | 3-Cl-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(3-chlorophenyl)-4-piperidinol | 526 | 0.18 (1:2 Hexane/EtOAc) | 3.39 | 1 | 18 |
| 379 | 2-Cl-Ph | 4-Cl-Ph | Et | 3-Cl-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl]-4-(3-chlorophenyl)-4-piperidinol | 554 | 0.42 (EtOAc) | 3.44 | 1 | 18 |
| 380 | 2-Cl-Ph | 4-Cl-Ph | nPr | 3-Cl-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl]-4-(3-chlorophenyl)-4-piperidinol | 568 | 0.41 (EtOAc) | 3.58 | 1 | 18 |
| 381 | 2-Cl-Ph | 4-Cl-Ph | H | 3-F-4-CF ₃ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-[3-fluoro-4-(trifluoromethyl)phenyl]-4-piperidinol | 578 | 0.22 (1:2 Hexane/EtOAc) | 3.53 | 1 | 18 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------------|--|---------------|-------------------------|---------------|-------------|-----------------------------|
| 382 | 2-Cl-Ph | 4-Cl-Ph | H | 3-F-4-Cl-Ph | 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-4-(3-fluoro-4-chlorophenyl)-4-piperidinol | 544 | 0.25 (1:2 Hexane/EtOAc) | 3.36 | 1 | 18 |
| 383 | 2-Cl-Ph | 4-Cl-Ph | H | 3-F-Ph | 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-4-(3-fluorophenyl)-4-piperidinol | 510 | 0.24 (1:2 Hexane/EtOAc) | 3.19 | 1 | 18 |
| 384 | 2-Cl-Ph | 4-Cl-Ph | Et | 3-F-Ph | 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl)-4-(3-fluorophenyl)-4-piperidinol | 538 | 0.43 (EtOAc) | 3.30 | 1 | 18 |
| 385 | 2-Cl-Ph | 4-Cl-Ph | nPr | 3-F-Ph | 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl)-4-(3-fluorophenyl)-4-piperidinol | 552 | 0.43 (EtOAc) | 3.41 | 1 | 18 |
| 386 | 2-Cl-Ph | 4-Cl-Ph | H | 6-methyl-2-pyridinyl | 1-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-4-(6-methyl-2-pyridinyl)-4-piperidinol | 507 | 0.32 (EtOAc) | 2.29 | 1 | 18 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------------------|---|---------------|-------------------------|---------------|-------------|-----------------------------|
| 387 | 2-Cl-Ph | 4-Cl-Ph | Et | 6-methyl-2-pyridinyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl]-4-(6-methyl-2-pyridinyl)-4-piperidinol | 535 | 0.27 (1:2 Hexane/EtOAc) | 2.75 | 1 | 18 |
| 388 | 2-Cl-Ph | 4-Cl-Ph | H | 3-Me-4-MeO-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(4-methoxy-3-methylphenyl)-4-piperidinol | 537 | 0.20 (1:2 Hexane/EtOAc) | 3.25 | 1 | 18 |
| 389 | 2-Cl-Ph | 4-Cl-Ph | H | 3-MeO-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(3-methoxyphenyl)-4-piperidinol | 522 | 0.24 (1:2 Hexane/EtOAc) | 3.12 | 1 | 18 |
| 390 | 2-Cl-Ph | 4-Cl-Ph | H | 3-thienyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(3-thienyl)-4-piperidinol | 498 | 0.22 (1:2 Hexane/EtOAc) | 3.10 | 1 | 18 |
| 391 | 2-Cl-Ph | 4-Cl-Ph | H | 4,6-dimethyl-2-pyrimidinyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(4,6-dimethyl-2-pyrimidinyl)-4-piperidinol | 522 | 0.09 (EtOAc) | 2.55 | 1 | 18 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC R _f (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|------------------------|--|---------------|------------------------------|---------------|-------------|-----------------------------|
| 392 | 2-Cl-Ph | 4-Cl-Ph | H | 4-CF ₃ O-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(4-trifluoromethoxyphenyl)-4-piperidinol | 576 | 0.18 (1:2 Hexane/EtOAc) | 3.48 | 1 | 18 |
| 393 | 2-Cl-Ph | 4-Cl-Ph | Et | 4-CF ₃ O-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl]-4-(4-trifluoromethoxyphenyl)-4-piperidinol | 604 | 0.39 (EtOAc) | 3.58 | 1 | 18 |
| 394 | 2-Cl-Ph | 4-Cl-Ph | nPr | 4-CF ₃ O-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl]-4-(4-trifluoromethoxyphenyl)-4-piperidinol | 618 | 0.40 (EtOAc) | 3.70 | 1 | 18 |
| 395 | 2-Cl-Ph | 4-Cl-Ph | Et | 4-CF ₃ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl]-4-(4-trifluoromethylphenyl)-4-piperidinol | 588 | 0.42 (EtOAc) | 3.55 | 1 | 18 |
| 396 | 2-Cl-Ph | 4-Cl-Ph | nPr | 4-CF ₃ -Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl]-4-(4-trifluoromethylphenyl)-4-piperidinol | 602 | 0.40 (EtOAc) | 3.66 | 1 | 18 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|-----------------|--|---------------|-------------------------|---------------|-------------|-----------------------------|
| 397 | 2-Cl-Ph | 4-Cl-Ph | Et | 4-Cl-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl]-4-(4-chlorophenyl)-4-piperidinol | 554 | 0.42 (EtOAc) | 3.48 | 1 | 17 |
| 398 | 2-Cl-Ph | 4-Cl-Ph | nPr | 4-Cl-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl]-4-(4-chlorophenyl)-4-piperidinol | 568 | 0.38 (EtOAc) | 3.57 | 1 | 17 |
| 399 | 2-Cl-Ph | 4-Cl-Ph | H | 4-F-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(4-fluorophenyl)-4-piperidinol | 510 | 0.25 (1:2 Hexane/EtOAc) | 3.18 | 1 | 17 |
| 400 | 2-Cl-Ph | 4-Cl-Ph | Et | 4-F-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl]carbonyl]-4-(4-fluorophenyl)-4-piperidinol | 538 | 0.36 (EtOAc) | 3.29 | 1 | 17 |
| 401 | 2-Cl-Ph | 4-Cl-Ph | nPr | 4-F-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-1H-imidazol-4-yl]carbonyl]-4-(4-fluorophenyl)-4-piperidinol | 552 | 0.36 (EtOAc) | 3.41 | 1 | 17 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------------|---|---------------|-------------------------|---------------|-------------|-----------------------------|
| 402 | 2-Cl-Ph | 4-Cl-Ph | H | 5-methyl-2-pyridinyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(5-methyl-2-pyridinyl)-4-piperidinol | 507 | 0.15 (1:2 Hexane/EtOAc) | 2.31 | 1 | 18 |
| 403 | 2-Cl-Ph | 4-Cl-Ph | H | 4-MeO-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(4-methoxyphenyl)-4-piperidinol | 522 | 0.21 (1:2 Hexane/EtOAc) | 3.10 | 1 | 17 |
| 404 | 2-Cl-Ph | 4-Cl-Ph | H | 4-MeS-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-[4-(methylsulfonyl)phenyl]-4-piperidinol | 538 | 0.18 (1:2 Hexane/EtOAc) | 3.29 | 1 | 18 |
| 405 | 2-Cl-Ph | 4-Cl-Ph | H | 4-methyl-2-pyridinyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(4-methyl-2-pyridinyl)-4-piperidinol | 521 | 0.18 (EtOAc) | 2.24 | 1 | 18 |
| 406 | 2-Cl-Ph | 4-Cl-Ph | H | Et | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-ethyl-4-piperidinol | 444 | 0.15 (1:2 Hexane/EtOAc) | 2.86 | 1 | 17 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|-----------------|--|---------------|-------------------------|---------------|-------------|-----------------------------|
| 407 | 2-Cl-Ph | 4-Cl-Ph | H | iso-butyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-iso-butyl-4-piperidinol | 472 | 0.10 (1:2 Hexane/EtOAc) | 3.24 | 1 | 17 |
| 408 | 2-Cl-Ph | 4-Cl-Ph | H | Me | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-methyl-4-piperidinol | 431 | 0.08 (1:2 Hexane/EtOAc) | 2.69 | 1 | 17 |
| 409 | 2-Cl-Ph | 4-Cl-Ph | H | n-butyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-butyl-4-piperidinol | 472 | 0.11 (1:2 Hexane/EtOAc) | 3.84 | 1 | 18 |
| 410 | 2-Cl-Ph | 4-Cl-Ph | H | n-pentyl | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-pentyl-4-piperidinol | 486 | 0.30 (EtOAc) | 3.45 | 1 | 17 |
| 411 | 2-Cl-Ph | 4-Cl-Ph | H | Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-phenyl-4-piperidinol | 474 | | 3.03 | 2 | 10, 11, 12 |

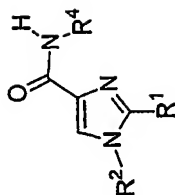
Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|-----------------|--|---------------|------------------|---------------|-------------|-----------------------------|
| 412 | 2,4-Cl ₂ -Ph | 4-MeO-Ph | H | Ph | 1-[[2-(2-chlorophenyl)-1-(4-methoxyphenyl)-1H-imidazol-4-yl]carbonyl]-4-phenyl-4-piperidinol | 522 | | 3.55 | 2 | 10, 11, 12 |
| 413 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | Ph | 1-[[2-(2,4-dichlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-phenyl-4-piperidinol | 526 | | 3.33 | 2 | 10, 11, 12 |
| 414 | 2-Me-Ph | 4-Cl-Ph | H | Ph | 1-[[2-(2-methylphenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-phenyl-4-piperidinol | 472 | | 2.90 | 2 | 10, 11, 12 |
| 415 | 2,4-Cl ₂ -Ph | 4-F-Ph | H | Ph | 1-[[2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazol-4-yl]carbonyl]-4-phenyl-4-piperidinol | 509 | | 3.03 | 2 | 10, 11, 12 |
| 416 | 2-Cl-Ph | 4-Cl-Ph | H | 4-Br-Ph | 1-[[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl]-4-(4-bromophenyl)-4-piperidinol | 570 | | 3.14 | 2 | 10, 11, 12 |

Table 13

| Entry No. | R ¹ | R ² | R ³ | R ¹⁴ | IUPAC name | MS m/z (MH+1) | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------------------|---|---------------|------------------|---------------|-------------|-----------------------------|
| 417 | 2-Cl-Ph | 4-Cl-Ph | H | benzyl | 1-{{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-benzyl-4-piperidinol} | 506 | | 2.98 | 2 | 10, 11, 12 |
| 418 | 2-Cl-Ph | 4-Cl-Ph | H | 3-CF ₃ -4-Cl-Ph | 1-{{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[4-chloro-3-(trifluoromethyl)phenyl]-4-piperidinol} | 594 | | 3.38 | 2 | 10, 11, 12 |
| 419 | 2-Cl-Ph | 4-Cl-Ph | H | 4-Cl-Ph | 1-{{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-(4-chlorophenyl)-4-piperidinol} | 526 | | 3.11 | 2 | 10, 11, 12 |
| 420 | 2-Cl-Ph | 4-Cl-Ph | H | 3-CF ₃ -Ph | 1-{{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-4-[3-(trifluoromethyl)phenyl]-4-piperidinol} | 560 | | 3.17 | 2 | 10, 11, 12 |

Table 14



| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|--------------------------------|----------------|----------------|---|---------------------------|--|----------------|-------------|-----------------------------|
| 421 | 2-Cl-Ph | 3-pyridinyl | cyclohexyl | 2-(2-chlorophenyl)-N-cyclohexyl-1-(3-pyridinyl)-1H-imidazole-4-carboxamide | 381.2 | 0.23 (4% MeOH in CH ₂ Cl ₂) | 2.71 | 1 | 8 |
| 422 | 2-Cl-3-pyridinyl | 4-F-Ph | 1-piperidinyl | 2-(2-chloro-3-pyridinyl)-1-(4-fluorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 400.3 | 0.19 (EtOAc) | 2.32 | 1 | 10, 11, 12 |
| 423 | 4-CF ₃ -3-pyridinyl | 4-Cl-Ph | 1-piperidinyl | 1-(4-chlorophenyl)-N-(1-piperidinyl)-2-[4-(trifluoromethyl)-3-pyridinyl]-1H-imidazole-4-carboxamide | 450.3 | 0.45 (10% MeOH in EtOAc) | 2.58 | 1 | 8 |
| 424 | 3-Me-2-pyridinyl | 4-Cl-Ph | 1-piperidinyl | 1-(4-chlorophenyl)-2-(3-methyl-2-pyridinyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 396.3 | 0.25 (EtOAc) | 2.27 | 1 | 8 |

Table 14

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|--------------------------------|---------------------|----------------------------|---|---------------------------|----------------------------|----------------|-------------|-----------------------------|
| 425 | 3-Me-4-pyridinyl | 4-Cl-Ph | 1-piperidinyl | 1-(4-chlorophenyl)-2-(3-methyl-4-pyridinyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 396.3 | 0.30 (2% MeOH in EtOAc) | 2.10 | 1 | 13, 14 |
| 426 | 4-CF ₃ -3-pyridinyl | 4-Cl-Ph | 2-CF ₃ -anilino | 1-(4-chlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-2-[4-(trifluoromethyl)-3-pyridinyl]-1H-imidazole-4-carbohydrazide hydrochloride | 525 | | 3.65 | 1 | 10, 11, 12 |
| 427 | 3-Me-2-thienyl | 4-Cl-Ph | 1-piperidinyl | 1-(4-chlorophenyl)-2-(3-methyl-2-thienyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 401.2 | 0.22 (67% EtOAc in hexane) | 2.8 | 1 | 6 |
| 428 | 2-furyl | 4-Cl-Ph | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-furyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 371.2 | 0.27 (80% EtOAc in hexane) | 2.57 | 1 | 6 |
| 429 | 2-Cl-Ph | 5-t-Bu-3-isoxazolyl | 1-piperidinyl | 1-(5-tert-butyl-3-isoxazolyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 428.2 | 0.12 (1:1 EtOAc/hexane) | 3.06 | 1 | 13, 14 |

Table 14

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|---------------------|----------------------------------|---|---------------------------|-------------------------|----------------|-------------|-----------------------------|
| 430 | 2-Cl-Ph | 5-t-Bu-3-isoxazolyl | cyclohexyl | 1-(5-tert-butyl-3-isoxazolyl)-2-(2-chlorophenyl)-N-cyclohexyl-1H-imidazole-4-carboxamide | 427.2 | 0.39 (1:1 EtOAc/hexane) | 3.68 | 1 | 13, 14 |
| 431 | 2-Cl-Ph | 5-t-Bu-3-isoxazolyl | 2-(S)-benzyloxy-1-(S)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-1-(5-tert-butyl-3-isoxazolyl)-2-(2-chlorophenyl)-1H-imidazole-4-carboxamide | 533.1 | 0.34 (1:1 EtOAc/hexane) | 3.89 | 1 | 13, 14 |
| 432 | 2-Cl-Ph | 3-quinoliny | 1-piperidinyl | 2-(2-chlorophenyl)-N-(1-piperidinyl)-1-(3-quinoliny)-1H-imidazole-4-carboxamide | 432.2 | 0.11 (EtOAc) | 2.61 | 1 | 13, 14 |
| 433 | 2-Cl-Ph | 3-quinoliny | cyclohexyl | 2-(2-chlorophenyl)-N-cyclohexyl-1-(3-quinoliny)-1H-imidazole-4-carboxamide | 431.2 | 0.44 (EtOAc) | 3.23 | 1 | 13, 14 |
| 434 | 2-Cl-Ph | 3-quinoliny | 2-(S)-benzyloxy-1-(S)-cyclohexyl | N-[(1S,2S)-2-(benzyloxy)cyclohexyl]-2-(2-chlorophenyl)-1-(3-quinoliny)-1H-imidazole-4-carboxamide | 537.1 | 0.46 (EtOAc) | 3.51 | 1 | 13, 14 |

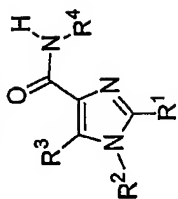
Table 14

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|------------------|------------------------------|--------------------------------|--|---------------------------|------------------|----------------|-------------|-----------------------------|
| 435 | 2-Cl-Ph | 5- <i>t</i> -Bu-3-isoxazolyl | 2-(S)-hydroxy-1-(S)-cyclohexyl | 1-(5- <i>tert</i> -butyl-3-isoxazolyl)-2-(2-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide | 443.2 | 0.43 (EtOAc) | 3.07 | 1 | 35 |
| 436 | 2-Cl-Ph | 3-quinolinyl | 2-(S)-hydroxy-1-(S)-cyclohexyl | 2-(2-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1-(3-quinolinyl)-1H-imidazole-4-carboxamide | 447.2 | 0.19 (EtOAc) | 2.65 | 1 | 35 |
| 437 | 2-Me-4-thiazolyl | 4-Cl-Ph | 1-piperidinyl | 1-(4-chlorophenyl)-2-(2-methyl-1,3-thiazol-4-yl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 402.2 | 0.21 (EtOAc) | 2.41 | 1 | 6 |
| 438 | 1-naphthyl | 4-Cl-Ph | 1-piperidinyl | 1-(4-chlorophenyl)-2-(1-naphthyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 431.2 | 0.42 (EtOAc) | 3.06 | 1 | 6 |
| 439 | 2-Cl-Ph | 1,3-thiazol-2-yl | 1-piperidinyl | 2-(2-chlorophenyl)-N-(1-piperidinyl)-1-(1,3-thiazol-2-yl)-1H-imidazole-4-carboxamide | 388.1 | 0.27 (EtOAc) | 2.46 | 1 | 13, 14 |

Table 14

| Entry No. | R ¹ | R ² | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|------------------|----------------|---|---------------------------|------------------|----------------|-------------|-----------------------------|
| 440 | 2-Cl-Ph | 1,3-thiazol-2-yl | cyclohexyl | 2-(2-chlorophenyl)-N-cyclohexyl-1-(1,3-thiazol-2-yl)-1H-imidazole-4-carboxamide | 387.1 | 0.52 (EtOAc) | 3.15 | 1 | 13, 14 |

Table 15



| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------|--|---------------------------|-------------------------|----------------|-------------|-----------------------------|
| 441 | 2-Cl-Ph | 4-Cl-benzyl | Me | cyclohexyl | 1-(4-chlorobenzyl)-2-(2-chlorophenyl)-N-cyclohexyl-5-methyl-1H-imidazole-4-carboxamide | 442.2 | | 2.65 | 1 | 8 |
| 442 | 2-Cl-Ph | 1-piperidinyl | H | 1-piperidinyl | 2-(2-chlorophenyl)-N,1-di(1-piperidinyl)-1H-imidazole-4-carboxamide | 388.3 | 0.10 (1:1 EtOAc/hexane) | 2.76 | 1 | 10, 11, 12 |
| 443 | 2-Cl-Ph | 1-piperidinyl | H | cyclohexyl | 2-(2-chlorophenyl)-N-cyclohexyl-1-(1-piperidinyl)-1H-imidazole-4-carboxamide | 387.3 | 0.38 (1:1 EtOAc/hexane) | 3.44 | 1 | 10, 11, 12 |
| 444 | 2-Cl-Ph | 4-morpholinyl | H | 1-piperidinyl | 2-(2-chlorophenyl)-1-(4-morpholinyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 390.4 | 0.13 (EtOAc) | 2.21 | 1 | 10, 11, 12 |

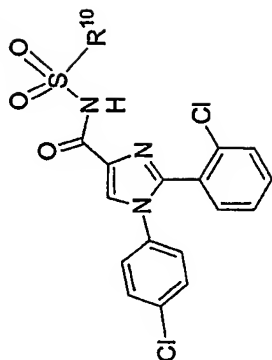
Table 15

| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|-----------------|----------------|----------------|--|---------------------------|-------------------------|----------------|-------------|-----------------------------|
| 445 | 2-Cl-Ph | 4-morpholinyl | H | cyclohexyl | 2-(2-chlorophenyl)-N-cyclohexyl-1-(4-morpholinyl)-1H-imidazole-4-carboxamide | 389.3 | 0.13 (1:1 EtOAc/hexane) | 2.87 | 1 | 10, 11, 12 |
| 446 | 2-Cl-Ph | cyclohexyl | H | 1-piperidinyl | 2-(2-chlorophenyl)-1-cyclohexyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 387.4 | 0.18 (EtOAc) | 2.60 | 1 | 10, 11, 12 |
| 447 | 2-Cl-Ph | cyclohexyl | H | cyclohexyl | 2-(2-chlorophenyl)-N,1-dicyclohexyl-1H-imidazole-4-carboxamide | 386.4 | 0.30 (1:1 EtOAc/hexane) | 3.23 | 1 | 10, 11, 12 |
| 448 | 2-Cl-Ph | 4-Me-cyclohexyl | H | cyclohexyl | 2-(2-chlorophenyl)-N-cyclohexyl-1-(4-methylcyclohexyl)-1H-imidazole-4-carboxamide | 400.4 | 0.38 (1:1 EtOAc/hexane) | 3.43 | 1 | 10, 11, 12 |
| 449 | 2-Cl-Ph | 4-Me-cyclohexyl | H | 1-piperidinyl | 2-(2-chlorophenyl)-1-(4-methylcyclohexyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 401.4 | 0.32 (EtOAc) | 2.83 | 1 | 10, 11, 12 |

Table 15

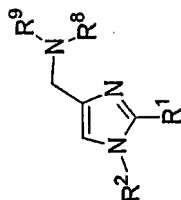
| Entry No. | R ¹ | R ² | R ³ | R ⁴ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min.) | HPLC method | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|----------------|---|---------------------------|-------------------------|----------------|-------------|-----------------------------|
| 450 | 2-Me-1-propyl | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-isobutyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 361.2 | 0.28 (EtOAc) | 2.43 | 1 | 6 |
| 451 | 2-Cl-Ph | 4-F-benzyl | Et | 1-piperidinyl | 2-(2-chlorophenyl)-5-ethyl-1-(4-fluorobenzyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 441.2 | 0.21 (EtOAc) | 2.75 | 1 | 13, 14 |
| 452 | 2-Cl-Ph | 4-MeO-PhCO | Et | 1-piperidinyl | 2-(2-chlorophenyl)-5-ethyl-1-(4-methoxybenzyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 467.2 | 0.24 (1:1 EtOAc/hexane) | 3.01 | 1 | 6 |
| 453 | benzyl | 4-Cl-Ph | H | 1-piperidinyl | 2-benzyl-1-(4-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 395.2 | 0.26 (EtOAc) | 2.75 | 1 | 6 |
| 454 | n-hexyl | 4-Cl-Ph | H | 1-piperidinyl | 1-(4-chlorophenyl)-2-hexyl-N-(1-piperidinyl)-1H-imidazole-4-carboxamide | 389.2 | 0.30 (EtOAc) | 3 | 1 | 6 |

Table 16



| Entry No. | R ¹⁰ | IUPAC name | MS m/z [MH ⁺] | LC-MS RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-----------------------|--|------------------------------|-------------------|----------------|-----------------------------------|
| 455 | Me | N-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)methanesulfonamide | 410 | 2.70 | 2 | 16 |
| 456 | 4-CF ₃ -Ph | N-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-4-(trifluoromethyl)benzenesulfonamide | 540 | 3.55 | 2 | 16 |
| 457 | Ph | N-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)benzenesulfonamide | 472 | 3.14 | 2 | 16 |
| 458 | 4-MeO-Ph | N-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl)-4-methoxybenzenesulfonamide | 502 | 3.22 | 2 | 16 |

Table 17

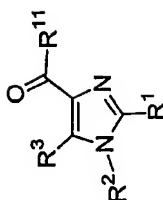


| Entry No. | R ¹ | R ² | R ⁸ | R ⁹ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|---------------------------|---|---------------------------|---------------------------|---------------|-------------|-----------------------------|
| 459 | 2-MeO-Ph | 4-Cl-Ph | H | 4-F-benzyl | N-[[1-(4-chlorophenyl)-2-(2-methoxyphenyl)-1H-imidazol-4-yl]methyl]-N-(4-fluorobenzyl)amine | 422 | 0.3 (88% EtOAc in hexane) | 2.48 | 1 | 33 |
| 460 | 2,4-Cl ₂ -Ph | 4-F-Ph | Me | cyclohexyl | N-cyclohexyl-N-[[2-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-1H-imidazol-4-yl]methyl]-N-methylamine | 432 | 0.19 (10% MeOH in hexane) | 2.65 | 1 | 34 |
| 461 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 4-F-benzyl | N-[[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]methyl]-N-(4-fluorobenzyl)amine | 460 | 0.33 (10% MeOH in EtOAc) | 2.88 | 1 | 33 |
| 462 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 4-CF ₃ -benzyl | N-[[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]methyl]-N-[4-(trifluoromethyl)benzyl]amine | 510 | 0.33 (5% MeOH in EtOAc) | 3.03 | 1 | 33 |

Table 17

| Entry No. | R ¹ | R ² | R ³ | IUPAC name | MS m/z [MH ⁺] | TLC Rf (solvent) | HPLC RT (min) | HPLC method | Synthesis Method of Ex. No. |
|-----------|-------------------------|----------------|----------------|---|---------------------------|--------------------------|---------------|-------------|-----------------------------|
| 463 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | trans-2-({[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]methyl}amino)cyclohexanol | 451 | 0.3 (33% MeOH in EtOAc) | 2.69 | 1 | 33 |
| 464 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | N-([1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]methyl)-N-cyclohexylamine | 434 | 0.31 (25% MeOH in EtOAc) | 2.83 | 1 | 33 |
| 465 | 2,4-Cl ₂ -Ph | 4-Cl-Ph | H | 1-([1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]methyl)-4-(4-methylphenyl)piperazine bis(trifluoroacetate) | 511 | | 2.94 | 1 | 34 |
| 466 | 2-Cl-Ph | 4-Cl-Ph | H | N-([2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]methyl)-N-cyclohexylamine | 401 | 0.35 (50% EtOAc in MeOH) | 2.32 | 1 | 33 |

Table 18



| Entry No. | R ¹ | R ² | R ³ | R ¹¹ | IUPAC Name | MS m/z (MH ⁺) | TLC Rf (solvent) | HPLC RT (min) (LC-MS) | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|-----------------|--|---------------------------|-------------------------|-----------------------|-----------------------------|
| 467 | 2-Cl-Ph | 4-Cl-Ph | Et | 2-thienyl | [2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl](2-thienyl)methanone | 427 | 0.13 (1:5 EtOAc/Hexane) | 3.93 | 31 |
| 468 | 2-Cl-Ph | 4-Cl-Ph | H | n-propyl | 1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-1-butanone | 359 | 0.49 (1:1 EtOAc/Hexane) | 3.30 | 29 |
| 469 | 2-Cl-Ph | 4-Cl-Ph | H | 1-methylpropyl | 1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-3-methyl-1-butanone | 373 | 0.53 (1:1 EtOAc/Hexane) | 3.47 | 29 |
| 470 | 2-Cl-Ph | 4-Cl-Ph | H | 1-methylpropyl | 1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-2-methyl-1-butanone | 373 | 0.56 (1:1 EtOAc/Hexane) | 3.47 | 29 |

Table 18

| Entry No. | R ¹ | R ² | R ³ | R ¹¹ | IUPAC Name | MS m/z (MH ⁺) | TLC Rf (solvent) | HPLC RT (min) (LC-MS) | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|-----------------|---|---------------------------|-------------------------|-----------------------|-----------------------------|
| 471 | 2-Cl-Ph | 4-Cl-Ph | H | n-pentyl | 1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-1-hexanone | 387 | 0.56 (1:1 EtOAc/Hexane) | 3.71 | 29 |
| 472 | 2-Cl-Ph | 4-Cl-Ph | H | cyclopentyl | [2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](cyclopentyl)methanone | 385 | 0.54 (1:1 EtOAc/Hexane) | 3.54 | 29 |
| 473 | 2-Cl-Ph | 4-Cl-Ph | H | cyclohexyl | [2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](cyclohexyl)methanone | 399 | 0.56 (1:1 EtOAc/Hexane) | 3.71 | 29 |
| 474 | 2-Cl-Ph | 4-Cl-Ph | H | 4-F-Ph | [2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](4-fluorophenyl)methanone | 411 | 0.58 (1:1 EtOAc/Hexane) | 3.57 | 29 |
| 475 | 2-Cl-Ph | 4-Cl-Ph | H | 4-Cl-Ph | (4-chlorophenyl)[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]methanone | 427 | 0.37 (1:3 EtOAc/Hexane) | 3.83 | 29 |

Table 18

| Entry No. | R ¹ | R ² | R ³ | R ¹¹ | IUPAC Name | MS m/z (MH ⁺) | TLC Rf (solvent) | HPLC RT (min) (LC-MS) | Synthesis Method of Ex. No. |
|-----------|----------------|----------------|----------------|-----------------|---|---------------------------|-------------------------|-----------------------|-----------------------------|
| 476 | 2-Cl-Ph | 4-Cl-Ph | H | 2-MeO-Ph | [2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-(3-methoxyphenyl)methanone | 423 | 0.20 (1:3 EtOAc/Hexane) | 3.52 | 29 |
| 477 | 2-Cl-Ph | 4-Cl-Ph | H | 4-MeO-Ph | [2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-(4-methoxyphenyl)methanone | 423 | 0.18 (1:3 EtOAc/Hexane) | 3.51 | 29 |
| 478 | 2-Cl-Ph | 4-Cl-Ph | H | Et | 1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-1-propanone | 345 | 0.42 (1:1 EtOAc/Hexane) | 3.10 | 29 |
| 479 | 2-Cl-Ph | 4-Cl-Ph | H | benzyl | 1-[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]-2-phenylethanone | 407 | 0.51 (1:1 EtOAc/Hexane) | 3.54 | 29 |
| 480 | 2-Cl-Ph | 4-Cl-Ph | H | Ph | [2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](phenyl)methanone | 393 | 0.5 (1:1 EtOAc/Hexane) | 3.48 | 29 |

Evaluation of Biological Activity

Evaluation of Compound's Efficacy on the Reduction of Food Intake in Lean Overnight Fasted Rats

5 Fasted-Refed Acute Feeding Assay

The purpose of this protocol is to determine the effect of a single dose of an unknown compound on food consumption of lean overnight fasted rats. The fasted-refed rat model is frequently used in the field of obesity to identify compounds with potential for anorectic effects. This animal model has been successfully used in the identification and characterization of the efficacy profile of compounds that are or have been used in the management of body weight in obese humans (*see, e.g.*, Balvet et al., Gen. Pharmacol. 13:293-297, 1982; Grignaschi et al., Br. J. Pharmacol. 127:1190-1194, 1999; McTavish and Heel, Drug 43:713-733, 1992; Rowland et al., Life Sci. 36:2295-2300, 1985).

15 A typical study includes 60-80 male rats (n=10/treatment group) with an average body weight of approximately 280 g. Rats are kept in standard animal rooms under controlled temperature and humidity and a 12/12 light dark cycle. Rats are single-housed in suspended cages with a mesh floor. Water and food are continuously available unless the animals are being fasted for the study.

20 The vehicle test: The rats are grouped based upon their performance on a vehicle test. The vehicle test is performed between 2 and 7 days before the efficacy test. The rats are fasted overnight during the dark phase (total of approx. 16-18 hrs). The animal is dosed with 0.5 mL deionized water. One hour after dosing, pre-weighed food jars are returned to the animal home cage. The rats are allowed one hour of feeding time. After 1 hour, the spillage is returned to the food jar and the amount of food consumed is determined. The rats are assigned to groups so that the mean and standard error of the mean of 1-hour food consumption are similar between groups.

25 The efficacy test: The rats are fasted overnight during the dark phase (total of approx. 16-18 hr). The animal is dosed with an assigned treatment (2 mg/ml). One hour after dosing, pre-weighed food jars are returned to the cage. Food intake is recorded 30, 60, 90, 180, and 240 minutes post-food return. At each time point, spillage is returned to the food jar and then the food jars are weighed. The amount of food consumed is determined for each time point. Difference between treatment group is determined using appropriate statistical analysis.

30 Compounds of the present invention were found to be active in this fasted-refed acute feeding assay. For example, when the imidazole derivative 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide was dosed at 10 mg/kg p.o., food consumption was reduced (relative to the food consumption observed for the

vehicle control group) by 34% to 62% when measured at time points from 30 to 240 minutes. Likewise, when the imidazole derivative 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[4-(trifluoromethyl)phenyl]-1*H*-imidazole-4-carbohydrazide hydrochloride was dosed at 10 mg/kg p.o., food consumption was reduced (relative to the food consumption observed for the vehicle control group) by 31% to 53% when measured at time points from 30 to 240 minutes.

Evaluation of Compound's Efficacy on the Reduction of Body Weight and Food and Water Consumption in Obese Zucker fa/fa Rats

Chronic Feeding Assay

The purpose of this protocol is to determine the effect of chronic administration of an unknown compound on body weight and food and water consumption in obese Zucker fa/fa rats. Obese Zucker fa/fa rats are frequently used in the determination of compound efficacy in the reduction of body weight. This animal model has been successfully used in the identification and characterization of the efficacy profile of compounds that are or have been used in the management of body weight in obese humans (*see, e.g.*, Al-Barazanji et al., *Obes Res.* 8:317-323, 2000; Assimacopoulos-Jeannet et al., *Am. J. Physiol.* 260(2 Pt 2):R278-283, 1991; Dryden et al., *Horm. Metab. Res.* 31:363-366, 1999; Edwards and Stevens, *Pharmacol. Biochem. Behav.* 47:865-872, 1994; Grinker et al., *Pharmacol. Biochem. Behav.* 12:265-275, 1980).

A typical study includes 60-80 male Zucker fa/fa (n=10/treatment group) with an average body weight of approximately 550 g. Rats are kept in standard animal rooms under controlled temperature and humidity and a 12/12 light dark cycle. Water and food are continuously available. Rats are single-housed in large rat shoeboxes containing grid floor. Animals are adapted to the grid floors and sham-dosed with study vehicle for at least four days before the recording of two-days baseline measurement of body weight and 24-hr food and water consumption. Rats are assigned to one of 6-8 treatment groups based upon their body weight on baseline. The groups are set up so that the mean and standard error of the mean of body weight were similar.

Animals are orally gavaged (2 mL/kg) daily before the dark phase of the LD/cycle for a pre-determined number of days (typically 6-14 days) with their assigned dose/compound. At this time, body weight, food and water consumption are measured. On the final day, animals are euthanized by CO₂ inhalation, and the body weight is measured.

Compounds of this invention were found to be active in this chronic feeding assay. For example, when the imidazole derivative 2-(2-chlorophenyl)-1-(4-chlorophenyl)-*N*-[(1*S*,2*S*)-2-hydroxycyclohexyl]-1*H*-imidazole-4-carboxamide was dosed once a day at 10 mg/kg p.o., on day 6 of treatment the increase in body weight from baseline was approximately 2.4%, representing approximately 50% reduction in body weight gain as compared to the vehicle control group, where

an approximately 4.6% increase in body weight from baseline was observed. Likewise, when the imidazole derivative 2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide hydrochloride was dosed once a day at 10 mg/kg p.o., on day 6 of treatment the increase in body weight from baseline was approximately 1.8%, representing
5 approximately 60% reduction in body weight gain as compared to the vehicle control group, where an approximately 4.6% increase in body weight from baseline was observed.

Measurement of brain exposure

Male obese Zucker fa/fa rats were administered compounds, typically at 10 mg/kg p.o.,
10 and then brains were collected at 2 hours post-dosing for determination of brain concentration. Brains were weighed and homogenized with 4 mL 10 mM ammonium acetate buffer (pH 3), and the brain tissue homogenate samples were extracted via protein precipitation with acetonitrile. Samples were vortexed, centrifuged, and analyzed by liquid chromatography utilizing mass spectrometer selective detection (LC/MS/MS) using the heated nebulizer interface. Samples were
15 quantitated using weighted ($1/x^2$) linear internal standard calibration curve. For example, when 1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-butyl-1H-imidazole-4-carboxamide was dosed at 10 mg/kg p.o., a brain homogenate exposure level of approximately 200 nM was determined; when 2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide was dosed at 10 mg/kg p.o., a brain
20 homogenate exposure level of approximately 200 nM was determined.

Demonstration of additional biological activities of the compounds of the present invention may be accomplished through *in vitro*, *ex vivo*, and *in vivo* assays that are well known in the art. For example, to demonstrate the efficacy of a pharmaceutical agent for the treatment of
25 obesity-related disorders such as diabetes, Syndrome X, or atherosclerotic disease and related disorders such as hypertriglyceridemia and hypercholesteremia, the following assays may be used.

Method for Measuring Blood Glucose Levels

db/db mice (obtained from Jackson Laboratories, Bar Harbor, ME) are bled (by either eye
30 or tail vein) and grouped according to equivalent mean blood glucose levels. They are dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test compound once daily for 14 days. At this point, the animals are bled again by eye or tail vein and blood glucose levels are determined. In each case, glucose levels are measured with a Glucometer Elite XL (Bayer Corporation, Elkhart, IN).

35

Method for Measuring Triglyceride Levels

hApoA1 mice (obtained from Jackson Laboratories, Bar Harbor, ME) are bled (by either eye or tail vein) and grouped according to equivalent mean serum triglyceride levels. They are dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test compound once daily for 8 days. The animals are then bled again by eye or tail vein, and serum triglyceride levels are determined. In each case, triglyceride levels are measured using a Technicon Axon Autoanalyzer (Bayer Corporation, Tarrytown, NY).

Method for Measuring HDL-Cholesterol Levels

To determine plasma HDL-cholesterol levels, hApoA1 mice are bled and grouped with equivalent mean plasma HDL-cholesterol levels. The mice are orally dosed once daily with vehicle or test compound for 7 days, and then bled again on day 8. Plasma is analyzed for HDL-cholesterol using the Synchron Clinical System (CX4) (Beckman Coulter, Fullerton, CA).

Method for Measuring Total Cholesterol, HDL-Cholesterol, Triglycerides, and Glucose Levels

In another *in vivo* assay, obese monkeys are bled, then orally dosed once daily with vehicle or test compound for 4 weeks, and then bled again. Serum is analyzed for total cholesterol, HDL-cholesterol, triglycerides, and glucose using the Synchron Clinical System (CX4) (Beckman Coulter, Fullerton, CA). Lipoprotein subclass analysis is performed by NMR spectroscopy as described by Oliver et al., (Proc. Natl. Acad. Sci. USA 98:5306-5311, 2001).

Method for Measuring an Effect on Cardiovascular Parameters

Cardiovascular parameters (e.g., heart rate and blood pressure) are also evaluated. SHR rats are orally dosed once daily with vehicle or test compound for 2 weeks. Blood pressure and heart rate are determined using a tail-cuff method as described by Grinsell et al., (Am. J. Hypertens. 13:370-375, 2000). In monkeys, blood pressure and heart rate are monitored as described by Shen et al., (J. Pharmacol. Exp. Therap. 278:1435-1443, 1996).

In addition, to demonstrate CNS activities of the compounds of the present invention, the following *in vivo* assays may be used.

Method for Testing Task Learning and Spatial Memory

The Morris Water Maze is routinely used to assess task learning and spatial memory (Jaspers et al., Neurosci. Lett. 117:149-153, 1990; Morris, J. Neurosci. Methods 11:47-60, 1984). In this assay, animals are placed in a water pool which is divided into quadrants. One platform is

hidden in one of the quadrants. The animal is placed in the water pool and is expected to locate the hidden platform within a predetermined time. During a number of training trials, the animal learns the location of the platform and escape from the pool. The animal receives multiple trials in this task. Total distance traveled, number of trials to locate platform, latency to find platform, and the swimming path is recorded for each animal. The animal's learning ability is measured by the length of time or number of trials required to find the hidden platform. Memory deficit or improvement is determined by the number of trials or the latency to find the platform at predetermined delay time after acquisition. Learning and memory may be measured by the number of times that the animal crosses the quadrant where the platform was located during the acquisition phase.

Method for Testing Drug Dependence

Self-administration in animals is a predictor of a compound's abuse potential in humans. Modifications to this procedure may also be used to identify compounds that prevent or block the reinforcing properties of drugs that have abuse potential. A compound that extinguishes the self-administration of a drug may prevent that drug's abuse or its dependence. (Ranaldi et al., Psychopharmacol. 161:442-448, 2002; Campbell et al., Exp. Clin. Psychopharmacol. 8:312-25, 2000). In a self-administration test, animals are placed in the operant chambers containing both an active and inactive lever. Each response on the active lever produces an infusion of either the test compound or a drug known to be self-administered. Presses on the inactive lever have no effect, but are also recorded. Animals are then trained to self-administer compound/drug over a set period of time by having drug access during each daily session. Illumination of the chamber house light signals the beginning of the session and the availability of the compound/drug. When the session ends, the house light is turned off. Initially, a drug infusion occurs with every press of the active lever. Once lever-pressing behavior has been established, the number of presses to produce a drug infusion is increased. After stable compound/drug self-administration is obtained, the effect of a second compound on the drug-reinforced behavior may be evaluated. Administration of this second compound prior to the session can either potentiate, extinguish, or produce no change to the self-administrating behavior. Tests are conducted every two days, and the order of the administration of the test compound doses is controlled.

Pharmaceutical Compositions

Based on the above tests, or other well known assays used to determine the efficacy for treatment of conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the

compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered may generally range from about 0.001 mg/kg to about 200 mg/kg, and preferably from about 0.01 mg/kg to about 200 mg/kg body weight per day. A unit dosage may contain from about 0.05 mg to about 1500 mg of active ingredient, and may be administered one or more times per day. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous, and parenteral injections, and use of infusion techniques may be from about 0.01 to about 200 mg/kg. The daily rectal dosage regimen may be from 0.01 to 200 mg/kg of total body weight. The transdermal concentration may be that required to maintain a daily dose of from 0.01 to 200 mg/kg.

Of course, the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age of the patient, the diet of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt thereof may be ascertained by those skilled in the art using conventional treatment tests.

The compounds of this invention may be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof in an appropriately formulated pharmaceutical composition. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for a particular condition or disease. Therefore, the present invention includes pharmaceutical compositions which are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound identified by the methods described herein, or a pharmaceutically acceptable salt or ester thereof. A pharmaceutically acceptable carrier is any carrier which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of a compound is that amount which produces a result or exerts an influence on the particular condition being treated. The compounds identified by the methods described herein may be administered with a pharmaceutically-acceptable carrier using any effective conventional dosage unit forms, including, for example, immediate and timed release preparations, orally, parenterally, topically, or the like.

For oral administration, the compounds may be formulated into solid or liquid preparations such as, for example, capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms may be a capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders such as acacia, cornstarch, or gelatin; disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum; lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example, talc, stearic acid, or magnesium, calcium or zinc stearate; dyes; coloring agents; and flavoring agents intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil, or coconut oil; or in a mineral oil such as

liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or *n*-propyl *p*-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

5 Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent, and preservative, flavoring and coloring agents.

10 The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which may be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions; an alcohol such as ethanol, isopropanol, or hexadecyl alcohol; glycols such as propylene glycol or polyethylene glycol; glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethyleneglycol) 400; an oil; a fatty acid; a fatty acid ester or glyceride; or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

20 Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum, and mineral oil. Suitable fatty acids include oleic acid, stearic acid, and isostearic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

30 The parenteral compositions of this invention may typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulation ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can

be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid may be used in the preparation of injectables.

A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such material are, for example, cocoa butter and polyethylene glycol.

Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (*see, e.g.,* U.S. Patent No. 5,023,252, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. For example, direct techniques for administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in U.S. Patent No. 5,011,472, incorporated herein by reference.

The compositions of the invention may also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Any of the compositions of this invention may be preserved by the addition of an antioxidant such as ascorbic acid or by other suitable preservatives. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

Commonly used pharmaceutical ingredients which may be used as appropriate to formulate the composition for its intended route of administration include: acidifying agents, for example, but are not limited to, acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid; and alkalinizing agents such as, but are not limited to, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, triethylamine.

Other pharmaceutical ingredients include, for example, but are not limited to, adsorbents (e.g., powdered cellulose and activated charcoal); aerosol propellants (e.g., carbon dioxide, CCl_2F_2 , $\text{F}_2\text{ClC}-\text{CClF}_2$ and CClF_3); air displacement agents (e.g., nitrogen and argon); antifungal preservatives (e.g., benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate); antimicrobial preservatives (e.g., benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal); antioxidants (e.g., ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite); binding materials (e.g., block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers); buffering agents (e.g., potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate); carrying agents (e.g., acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection); chelating agents (e.g., edetate disodium and edetic acid); colorants (e.g., FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8,

caramel and ferric oxide red); clarifying agents (e.g., bentonite); emulsifying agents (but are not limited to, acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate); encapsulating agents (e.g., gelatin and cellulose acetate phthalate); flavorants (e.g., anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin); humectants (e.g., glycerin, propylene glycol and sorbitol); levigating agents (e.g., mineral oil and glycerin); oils (e.g., arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil); ointment bases (e.g., lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment); penetration enhancers (transdermal delivery) (e.g., monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas); plasticizers (e.g., diethyl phthalate and glycerin); solvents (e.g., alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation); stiffening agents (e.g., cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax); suppository bases (e.g., cocoa butter and polyethylene glycols (mixtures)); surfactants (e.g., benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate); suspending agents (e.g., agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum); sweetening e.g., aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose); tablet anti-adherents (e.g., magnesium stearate and talc); tablet binders (e.g., acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch); tablet and capsule diluents (e.g., dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch); tablet coating agents (e.g., liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac); tablet direct compression excipients (e.g., dibasic calcium phosphate); tablet disintegrants (e.g., alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch); tablet glidants (e.g., colloidal silica, corn starch and talc); tablet lubricants (e.g., calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate); tablet/capsule opaquants (e.g., titanium dioxide); tablet polishing agents (e.g., carnuba wax and white wax); thickening agents (e.g., beeswax, cetyl alcohol and paraffin); tonicity agents (e.g., dextrose and sodium chloride);

viscosity increasing agents (e.g., alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth); and wetting agents (e.g., heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

5 The compounds identified by the methods described herein may be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compounds of this invention can be combined with known anti-obesity, or with known antidiabetic or other indication agents, and the like, as well as with admixtures and combinations thereof.

10 The compounds identified by the methods described herein may also be utilized, in free base form or in compositions, in research and diagnostics, or as analytical reference standards, and the like. Therefore, the present invention includes compositions which are comprised of an inert carrier and an effective amount of a compound identified by the methods described herein, or a salt or ester thereof. An inert carrier is any material which does not interact with the compound to be carried and which lends support, means of conveyance, bulk, traceable material, and the like to the compound to be carried. An effective amount of compound is that amount which produces a result or exerts an influence on the particular procedure being performed.

15 Formulations suitable for subcutaneous, intravenous, intramuscular, and the like; suitable pharmaceutical carriers; and techniques for formulation and administration may be prepared by any of the methods well known in the art (*see, e.g.,* Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 20th edition, 2000)

20 The following examples are presented to illustrate the invention described herein, but should not be construed as limiting the scope of the invention in any way.

25 **Capsule Formulation**

A capsule formula is prepared from:

| | |
|----------------------------|--------|
| Compound of this invention | 40 mg |
| Starch | 109 mg |
| Magnesium stearate | 1 mg |

30 The components are blended, passed through an appropriate mesh sieve, and filled into hard gelatin capsules.

Tablet Formulation

35 A tablet is prepared from:

| | |
|-----------------------------|--------|
| Compound of this invention | 25 mg |
| Cellulose, microcrystalline | 200 mg |
| Colloidal silicon dioxide | 10 mg |
| Stearic acid | 5.0 mg |

5

The ingredients are mixed and compressed to form tablets. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

10 Sterile IV Solution

A 5 mg/ml solution of the desired compound of this invention is made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1-2 mg/ml with sterile 5% dextrose and is administered as an IV infusion over 60 minutes.

15 Intramuscular suspension

The following intramuscular suspension is prepared:

| | |
|-------------------------------|----------|
| Compound of this invention | 50 mg/ml |
| Sodium carboxymethylcellulose | 5 mg/ml |
| 20 TWEEN 80 | 4 mg/ml |
| Sodium chloride | 9 mg/ml |
| Benzyl alcohol | 9 mg/ml |

The suspension is administered intramuscularly.

25

Hard Shell Capsules

A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

30

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed
35 and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and

sorbitol to prepare a water miscible medicine mix.

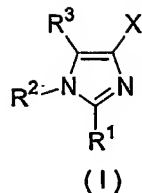
Immediate Release Tablets/Capsules

5 These are solid oral dosage forms made by conventional and novel processes. These units
are taken orally without water for immediate dissolution and delivery of the medication. The
active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and
sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid
state extraction techniques. The drug compounds may be compressed with viscoelastic and
thermoelastic sugars and polymers or effervescent components to produce porous matrices
10 intended for immediate release, without the need of water.

The structures, materials, compositions, and methods described herein are intended to be
representative examples of the invention, and it will be understood that the scope of the invention
is not limited by the scope of the examples. Those skilled in the art will recognize that the
15 invention may be practiced with variations on the disclosed structures, materials, compositions and
methods, and such variations are regarded as within the ambit of the invention.

What is claimed:

1. A compound of Formula I,



wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, (C₁-C₆)alkyl sulfonyl, (C₁-C₆)alkyl sulfonyl-amino, (C₁-C₆)alkyl carbonyl-amino, (C₁-C₆)alkyl amino-carbonyl-amino, or phenyl,

(C₂-C₆)alkyl,

cyclohexyl optionally substituted with (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or with one or more fluorine,

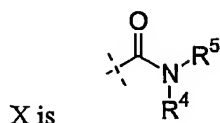
1-naphthyl or 2-naphthyl optionally substituted with halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano,

benzyl optionally substituted on the phenyl ring with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano,

a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with fluorine, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano, and

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or phenyl;

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;



where R⁴ is hydrogen or (C₁-C₆)alkyl;

R⁵ is selected from

(C₂-C₉)alkyl or (C₇-C₁₁)bicycloalkyl, each of which may optionally be substituted with one or more phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-amino, bis[(C₁-C₃)alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, 2,3-dihydro-1,4-benzodioxin-2-yl, hydroxy-substituted (C₁-C₆)alkyl, or fluorine,

benzyl, 2-phenyl-ethyl, benzocyclohexyl, or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy (C₁-C₆)alkyl, and optionally substituted on the phenyl ring with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, or nitro,

piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with (C₁-C₆)alkyl, hydroxy-substituted (C₁-C₆)alkyl, (C₁-C₃)alkoxy-substituted (C₁-C₃)alkyl, benzyl, or phenyl optionally substituted with one or more of (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or halogen,

-NR⁶R⁷

where R⁶ is hydrogen or (C₁-C₆)alkyl;

R⁷ is (C₁-C₉)alkyl, or phenyl optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy-substituted (C₁-C₆)alkyl, (C₁-C₃)alkoxy-substituted (C₁-C₃)alkyl, phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom; or

R⁶ and R⁷, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more (C₁-C₆)alkyl, (C₁-

C₆)alkoxy, hydroxy-substituted (C₁-C₃)alkyl, (C₁-C₃)alkoxy-substituted (C₁-C₃)alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

or

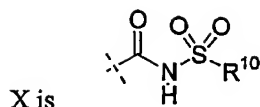
5

R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of fluorine, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-amino, bis[(C₁-C₃)alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C₁-C₆)alkyl, phenyl-substituted (C₁-C₆)alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more (C₁-C₆)alkyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

10

15

or



where R¹⁰ is (C₁-C₉)alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, or a fluorine atom, or

20

phenyl, benzocyclohexyl, or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, trifluoromethyl, benzyloxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halogen;

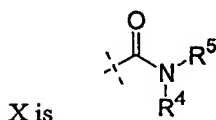
25

and pharmaceutical salts and esters thereof.

2. The compound of Claim 1, wherein

30

R¹, R², and R³ are defined as in Claim 1;



where R^4 is hydrogen or (C_1-C_6) alkyl;

R^5 is selected from

(C_2-C_9) alkyl or (C_7-C_{11}) bicycloalkyl, each of which may optionally be substituted with one or more phenyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, (C_1-C_6) alkyl-amino, bis[(C_1-C_3) alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, 2,3-dihydro-1,4-benzodioxin-2-yl, hydroxy-substituted (C_1-C_6) alkyl, or fluorine,

benzyl, 2-phenyl-ethyl, benzocyclohexyl, or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy (C_1-C_6) alkyl, and optionally substituted on the phenyl ring with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, or nitro,

piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with (C_1-C_6) alkyl, hydroxy-substituted (C_1-C_6) alkyl, (C_1-C_3) alkoxy-substituted (C_1-C_3) alkyl, benzyl, or phenyl optionally substituted with one or more of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or halogen,

$-NR^6R^7$

where R^6 is hydrogen or (C_1-C_6) alkyl;

R^7 is (C_1-C_9) alkyl, or phenyl optionally substituted with one or more of (C_1-C_6) alkyl, hydroxy-substituted (C_1-C_6) alkyl, (C_1-C_3) alkoxy-substituted (C_1-C_3) alkyl, phenyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom; or

R^6 and R^7 , taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more (C_1-C_6) alkyl, (C_1-C_6) alkoxy, hydroxy-substituted (C_1-C_3) alkyl, (C_1-C_3) alkoxy-substituted (C_1-C_3) alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

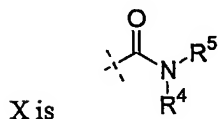
or

R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of fluorine, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-amino, bis[(C₁-C₃)alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C₁-C₆)alkyl, phenyl-substituted (C₁-C₆)alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more (C₁-C₆)alkyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

3. The compound of Claim 2, wherein

R¹, R², and R³ are defined as in Claim 1;



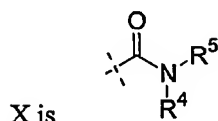
where

R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of fluorine, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-amino, bis[(C₁-C₃)alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C₁-C₆)alkyl, phenyl-substituted (C₁-C₆)alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more (C₁-C₆)alkyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

4. The compound of Claim 3, wherein

R¹, R², and R³ are defined as in Claim 1;



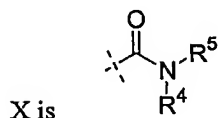
where

R⁴ and R⁵, taken together with the nitrogen atom to which they are attached,
 5 form a piperidin-1-yl or piperazin-1-yl group optionally substituted with one or more of
 fluorine, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, (C₁–C₆)alkyl-amino, bis[(C₁–C₃)alkyl]-amino,
 trifluoromethyl, hydroxy, hydroxy-substituted (C₁–C₆)alkyl, phenyl-substituted (C₁–
 C₆)alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic
 radical, or phenyl optionally substituted with one or more (C₁–C₆)alkyl, hydroxy,
 10 benzyloxy, (C₁–C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

5. The compound of Claim 4, wherein

15 R¹, R², and R³ are defined as in Claim 1;



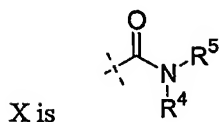
20 where

R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a
 piperazin-1-yl group optionally substituted at the 4-position with one or more of (C₁–
 C₆)alkyl, (C₁–C₆)alkyl-amino, bis[(C₁–C₃)alkyl]-amino, hydroxy-substituted (C₁–C₆)alkyl,
 phenyl-substituted (C₁–C₆)alkyl, a 5- to 10-membered aromatic monocyclic or bicyclic
 25 heterocyclic radical, or phenyl optionally substituted with one or more (C₁–C₆)alkyl,
 hydroxy, benzyloxy, (C₁–C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

6. The compound of Claim 5, wherein

30 R¹, R², and R³ are defined as in Claim 1;



where

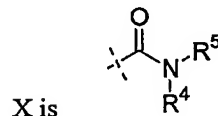
5 R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl group optionally substituted at the 4-position with one or more of (C₁–C₆)alkyl, hydroxy-substituted (C₁–C₆)alkyl, phenyl-substituted (C₁–C₆)alkyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, or phenyl optionally substituted with one or more (C₁–C₆)alkyl, hydroxy, (C₁–C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

10

and pharmaceutical salts and esters thereof.

7. The compound of Claim 6, wherein

15 R^1, R^2 , and R^3 are defined as in Claim 1;



where

20 R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl group optionally substituted at the 4-position with one or more of (C₁–C₆)alkyl, hydroxy-substituted (C₁–C₆)alkyl, benzyl, or phenyl optionally substituted with one or more (C₁–C₆)alkyl, hydroxy, (C₁–C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

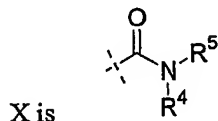
25

and pharmaceutical salts and esters thereof.

8. The compound of Claim 7, wherein

30 R¹ and R² are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, (C₁–C₆)alkyl, (C₁–
C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;



where

R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl group optionally substituted at the 4-position with one or more of (C₁-C₆)alkyl, hydroxy-substituted (C₁-C₆)alkyl, benzyl, or phenyl optionally substituted with one or more (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

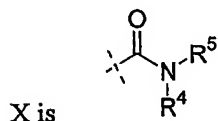
and pharmaceutical salts and esters thereof.

9. The compound of Claim 8, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



where

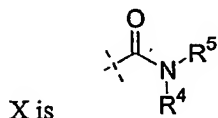
R⁴ and R⁵, taken together with the nitrogen atom to which they are attached, form a piperazin-1-yl group optionally substituted at the 4-position with one or more of (C₁-C₆)alkyl, hydroxy-substituted (C₁-C₆)alkyl, benzyl, or phenyl optionally substituted with one or more (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

10. The compound of Claim 4, wherein

R^1 , R^2 , and R^3 are defined as in Claim 1;

5



where

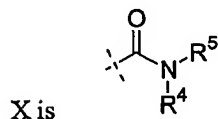
R^4 and R^5 , taken together with the nitrogen atom to which they are attached,
 10 form a piperidin-1-yl group optionally substituted with one or more of fluorine, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, (C₁–C₆)alkyl-amino, bis[(C₁–C₃)alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C₁–C₆)alkyl, phenyl-substituted (C₁–C₆)alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical, or phenyl optionally substituted with one or more (C₁–C₆)alkyl, hydroxy, benzyloxy, (C₁–C₆)alkoxy,
 15 trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

11. The compound of Claim 10, wherein

20

R^1 , R^2 , and R^3 are defined as in Claim 1;



25

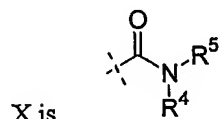
where

R^4 and R^5 , taken together with the nitrogen atom to which they are attached,
 form a piperidin-1-yl group optionally substituted at the 4-position with one or more of
 fluorine, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, (C₁–C₆)alkyl-amino, bis[(C₁–C₃)alkyl]-amino,
 trifluoromethyl, hydroxy, hydroxy-substituted (C₁–C₆)alkyl, phenyl-substituted (C₁–
 30 C₆)alkyl, cyano, a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic
 radical, or phenyl optionally substituted with one or more (C₁–C₆)alkyl, hydroxy,
 benzyloxy, (C₁–C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

12. The compound of Claim 11, wherein

R^1 , R^2 , and R^3 are defined as in Claim 1;



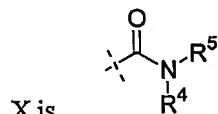
where

R^4 and R^5 , taken together with the nitrogen atom to which they are attached, form a piperidin-1-yl group optionally substituted at the 4-position with one or more of fluorine, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkyl-amino, bis[(C_1-C_3) alkyl]-amino, trifluoromethyl, hydroxy, hydroxy-substituted (C_1-C_6) alkyl, phenyl-substituted (C_1-C_6) alkyl, cyano, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, or phenyl optionally substituted with one or more (C_1-C_6) alkyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, or halogen;

and pharmaceutical salts and esters thereof.

13. The compound of Claim 12, wherein

R^1 , R^2 , and R^3 are defined as in Claim 1;



where

R^4 and R^5 , taken together with the nitrogen atom to which they are attached, form a 4-hydroxy-piperidin-1-yl group optionally also substituted at the 4-position with (C_1-C_6) alkyl, phenyl-substituted (C_1-C_6) alkyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, or phenyl optionally substituted with one or more (C_1-C_6) alkyl, hydroxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, or halogen;

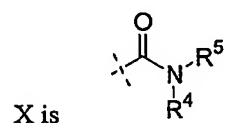
and pharmaceutical salts and esters thereof.

14. The compound of Claim 13, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, (C_1-C_6) alkyl, benzyl, chloro, or bromo;



where

R^4 and R^5 , taken together with the nitrogen atom to which they are attached, form a 4-hydroxy-piperidin-1-yl group optionally also substituted at the 4-position with (C_1-C_6) alkyl, phenyl-substituted (C_1-C_6) alkyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, or phenyl optionally substituted with one or more (C_1-C_6) alkyl, hydroxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, or halogen;

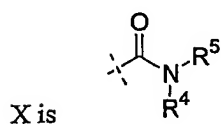
and pharmaceutical salts and esters thereof.

15. The compound of Claim 14, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



where

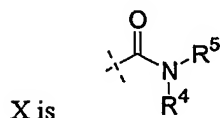
R^4 and R^5 , taken together with the nitrogen atom to which they are attached, form a 4-hydroxy-piperidin-1-yl group optionally also substituted at the 4-position with (C₁-C₆)alkyl, phenyl-substituted (C₁-C₆)alkyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, or phenyl optionally substituted with one or more (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or halogen;

and pharmaceutical salts and esters thereof.

16. The compound of Claim 15, wherein

R^1 and R^2 are identical or different and are selected from a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



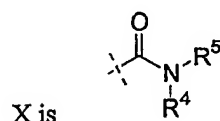
where

R^4 and R^5 , taken together with the nitrogen atom to which they are attached, form a 4-hydroxy-piperidin-1-yl group also substituted at the 4-position with (C₁-C₆)alkyl or with phenyl optionally substituted with one or more (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or halogen;

and pharmaceutical esters thereof.

17. The compound of Claim 2, wherein

R^1 , R^2 , and R^3 are defined as in Claim 1;



where R⁴ is hydrogen or (C₁-C₆)alkyl;

R⁵ is selected from

5 (C₂-C₉)alkyl or (C₇-C₁₁)bicycloalkyl, each of which may optionally be substituted with one or more phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-amino, bis[(C₁-C₃)alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, 2,3-dihydro-1,4-benzodioxin-2-yl, hydroxy-substituted (C₁-C₆)alkyl, or fluorine,

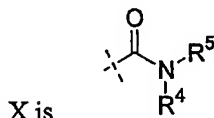
10 benzyl, 2-phenyl-ethyl, benzocyclohexyl, or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy (C₁-C₆)alkyl, and optionally substituted on the phenyl ring with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, or nitro,

15 piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with (C₁-C₆)alkyl, hydroxy-substituted (C₁-C₆)alkyl, (C₁-C₃)alkoxy-substituted (C₁-C₃)alkyl, benzyl, or phenyl optionally substituted with one or more of (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or
20 halogen;

and pharmaceutical salts and esters thereof.

25 18. The compound of Claim 17, wherein

R¹, R², and R³ are defined as in Claim 1;



30

where R⁴ is hydrogen or (C₁-C₆)alkyl;

R⁵ is selected from

(C₂-C₉)alkyl, optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, (C₁-C₆)alkyl-amino, bis[(C₁-C₃)alkyl]-amino, 1-piperidinyl, 1-pyrrolidinyl, hydroxy-substituted (C₁-C₆)alkyl, or fluorine,

5 benzyl, 2-phenyl-ethyl, benzocyclohexyl, or benzocyclopentyl, each of which may optionally be substituted on one of the alkyl carbons with hydroxy, and optionally substituted on the phenyl ring with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, or nitro,

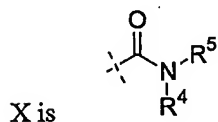
10 piperidin-4-yl, optionally substituted on the nitrogen atom with (C₁-C₆)alkyl, hydroxy-substituted (C₁-C₆)alkyl, (C₁-C₃)alkoxy-substituted (C₁-C₃)alkyl, benzyl, or phenyl optionally substituted with one or more of (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, nitro, or halogen;

15 and pharmaceutical salts and esters thereof.

19. The compound of Claim 17, wherein

R¹, R², and R³ are defined as in Claim 1;

20



where R⁴ is hydrogen or (C₁-C₆)alkyl;

25 R⁵ is selected from

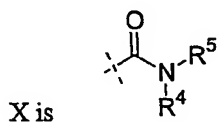
cyclopentyl, cyclohexyl, benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which is substituted on one alkyl carbon with hydroxy, and optionally substituted on the phenyl ring, if present in R⁵, with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano;

30

and pharmaceutical salts and esters thereof.

20. The compound of Claim 17, wherein

R¹, R², and R³ are defined as in Claim 1;



5 where R⁴ is hydrogen;

R⁵ is selected from

2-hydroxycyclopentyl, 2-hydroxycyclohexyl, 1-(hydroxymethyl)cyclopentyl, 1-hydroxy-2,3-dihydro-1H-inden-2-yl, 2-hydroxy-2,3-dihydro-1H-inden-1-yl, 3-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl, or 2-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl;

10

and pharmaceutical salts and esters thereof.

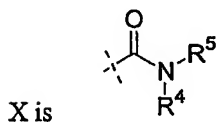
15 21. The compound of Claim 17, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, (C₁-C₆)alkyl sulfonyl, (C₁-C₆)alkyl sulfonyl-amino, (C₁-C₆)alkyl carbonyl-amino, (C₁-C₆)alkyl amino-carbonyl-amino, or phenyl;

20

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;



25

where R⁴ is hydrogen;

R⁵ is selected from

2-hydroxycyclopentyl, 2-hydroxycyclohexyl, 1-(hydroxymethyl)cyclopentyl, 1-hydroxy-2,3-dihydro-1H-inden-2-yl, 2-hydroxy-2,3-dihydro-1H-inden-1-yl, 3-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl, or 2-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl;

30

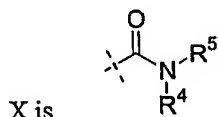
and pharmaceutical salts and esters thereof.

22. The compound of Claim 17, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;



where R⁴ is hydrogen;

R⁵ is selected from

2-hydroxycyclopentyl, 2-hydroxycyclohexyl, 1-(hydroxymethyl)cyclopentyl, 1-hydroxy-2,3-dihydro-1H-inden-2-yl, 2-hydroxy-2,3-dihydro-1H-inden-1-yl, 3-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl, or 2-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl;

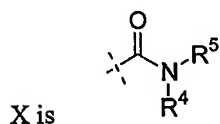
and pharmaceutical esters thereof.

23. The compound of Claim 17, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



where R⁴ is hydrogen;

R⁵ is selected from

5 2-hydroxycyclopentyl, 2-hydroxycyclohexyl, 1-(hydroxymethyl)cyclopentyl, 1-hydroxy-2,3-dihydro-1H-inden-2-yl, 2-hydroxy-2,3-dihydro-1H-inden-1-yl, 3-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl, or 2-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl;

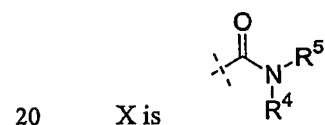
10 and pharmaceutical esters thereof.

24. The compound of Claim 17, wherein

R¹ and R² are identical or different and are selected from

15 a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



where R⁴ is hydrogen;

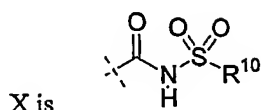
R⁵ is selected from

25 (R,R)-2-hydroxycyclopentyl, (R,R)-2-hydroxycyclohexyl, (S,S)-2-hydroxycyclopentyl, or (S,S)-2-hydroxycyclohexyl;

and pharmaceutical esters thereof.

30 25. The compound of Claim 1, wherein

R¹, R², and R³ are defined as in Claim 1;



where R¹⁰ is (C₁–C₉)alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C₁–C₆)alkoxy, or a fluorine atom, or

5

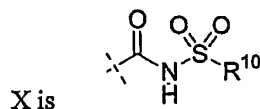
phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, trifluoromethyl, benzyloxy, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, or halogen;

10 and pharmaceutical salts and esters thereof.

26. The compound of Claim 25, wherein

R¹, R², and R³ are defined as in Claim 1;

15



where R¹⁰ is (C₁–C₉)alkyl optionally substituted with one or more hydroxy or fluorine, or

20

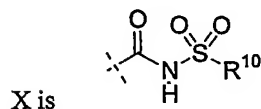
phenyl, optionally substituted with one or more of a hydroxy, trifluoromethyl, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, or halogen;

and pharmaceutical salts and esters thereof.

25

27. The compound of Claim 26, wherein

R¹, R², and R³ are defined as in Claim 1;



30

where R¹⁰ is (C₁–C₉)alkyl, or

phenyl, optionally substituted with one or more of a hydroxy, trifluoromethyl,
(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halogen;

5 and pharmaceutical salts and esters thereof.

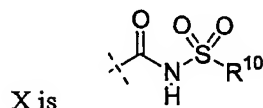
28. The compound of Claim 27, wherein

R¹ and R² are identical or different and are selected from

10 a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, (C₁-C₆)alkyl sulfonyl, (C₁-C₆)alkyl sulfonyl-amino, (C₁-C₆)alkyl carbonyl-amino, (C₁-C₆)alkyl amino-carbonyl-amino, or phenyl;

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;

15



where R¹⁰ is (C₁-C₉)alkyl, or

20 phenyl, optionally substituted with one or more of a hydroxy, trifluoromethyl,
(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halogen;

and pharmaceutical salts and esters thereof.

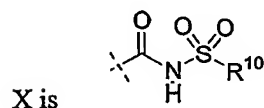
25 29. The compound of Claim 28, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano;

30

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;



where R¹⁰ is (C₁-C₉)alkyl, or

phenyl, optionally substituted with one or more of a hydroxy, trifluoromethyl,
(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halogen;

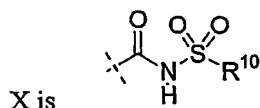
and pharmaceutical salts and esters thereof.

30. The compound of Claim 29, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



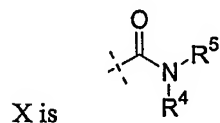
where R¹⁰ is (C₁-C₉)alkyl, or

phenyl, optionally substituted with one or more of a hydroxy, trifluoromethyl,
(C₁-C₆)alkyl, (C₁-C₆)alkoxy, or halogen;

and pharmaceutical salts and esters thereof.

31. The compound of Claim 1, wherein

R¹, R², and R³ are defined as in Claim 1;



where R⁴ is hydrogen;

R⁵ is



where R^6 is hydrogen or (C_1-C_6) alkyl;

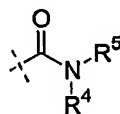
R^7 is (C_1-C_9) alkyl, or phenyl optionally substituted with one or more of (C_1-C_6) alkyl, hydroxy-substituted (C_1-C_6) alkyl, (C_1-C_3) alkoxy-substituted (C_1-C_3) alkyl, phenyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom, or

R^6 and R^7 , taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more (C_1-C_6) alkyl, (C_1-C_6) alkoxy, hydroxy-substituted (C_1-C_3) alkyl, (C_1-C_3) alkoxy-substituted (C_1-C_3) alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

and pharmaceutical salts and esters thereof.

32. The compound of Claim 31, wherein

R^1 , R^2 , and R^3 are defined as in Claim 1;



X is

where R^4 is hydrogen;

R^5 is



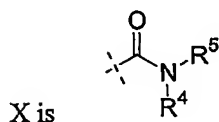
where

R^6 and R^7 , taken together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic ring which is optionally substituted by one or more (C_1-C_6) alkyl, (C_1-C_6) alkoxy, hydroxy-substituted (C_1-C_3) alkyl, (C_1-C_3) alkoxy-substituted (C_1-C_3) alkyl, benzyl, phenyl, hydroxy, benzyloxy, or fluorine;

and pharmaceutical salts and esters thereof.

33. The compound of Claim 32, wherein

R^1 , R^2 , and R^3 are defined as in Claim 1;



where R^4 is hydrogen;

10 R^5 is 1-piperidinyl, 1-pyrrolidinyl, 1-azepanyl, (2R)-2-(methoxymethyl)-1-pyrrolidinyl, (2S)-2-(methoxymethyl)-1-pyrrolidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, or hexahydrocyclopenta[c]pyrrol-2(1H)-yl;

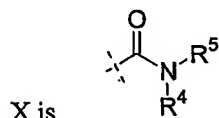
and pharmaceutical salts thereof.

15 34. The compound of Claim 33, wherein

R^1 and R^2 are identical or different and are selected from

20 a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, (C_1-C_6) alkyl sulfonyl, (C_1-C_6) alkyl sulfonyl-amino, (C_1-C_6) alkyl carbonyl-amino, (C_1-C_6) alkyl amino-carbonyl-amino, or phenyl;

R^3 is hydrogen, (C_1-C_6) alkyl, benzyl, chloro, or bromo;



where R^4 is hydrogen;

30 R^5 is 1-piperidinyl, 1-pyrrolidinyl, 1-azepanyl, (2R)-2-(methoxymethyl)-1-pyrrolidinyl, (2S)-2-(methoxymethyl)-1-pyrrolidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, or hexahydrocyclopenta[c]pyrrol-2(1H)-yl;

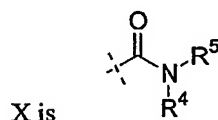
and pharmaceutical salts thereof.

35. The compound of Claim 34, wherein

5 R^1 and R^2 are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, (C_1-C_6) alkyl, benzyl, chloro or bromo;

10



where R^4 is hydrogen;

15 R^5 is 1-piperidinyl, 1-pyrrolidinyl, 1-azepanyl, (2R)-2-(methoxymethyl)-1-pyrrolidinyl,
(2S)-2-(methoxymethyl)-1-pyrrolidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, or
hexahydrocyclopenta[c]pyrrol-2(1H)-yl;

and pharmaceutical salts thereof.

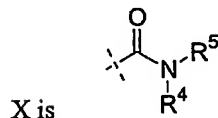
20

36. The compound of Claim 35, wherein

R^1 and R^2 are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano;

25

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



30

where R^4 is hydrogen;

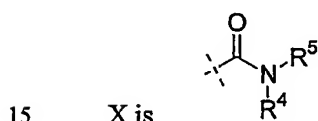
R⁵ is 1-piperidinyl, 1-pyrrolidinyl, 1-azepanyl, (2R)-2-(methoxymethyl)-1-pyrrolidinyl, (2S)-2-(methoxymethyl)-1-pyrrolidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, or hexahydrocyclopenta[c]pyrrol-2(1H)-yl;

5 and pharmaceutical salts and esters thereof.

37. The compound of Claim 36, wherein

10 R¹ and R² are identical or different and are selected from a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



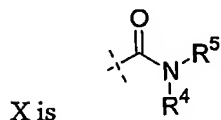
where R⁴ is hydrogen;

R⁵ is 1-piperidinyl, 1-pyrrolidinyl, or 1-azepanyl;

20 and pharmaceutical salts thereof.

38. The compound of Claim 31, wherein

25 R¹, R², and R³ are defined as in Claim 1;



where R⁴ is hydrogen;

R⁵ is



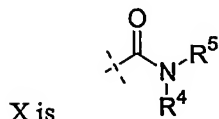
where R^6 is hydrogen or (C_1-C_6) alkyl;

R^7 is (C_1-C_9) alkyl, or phenyl optionally substituted with one or more of (C_1-C_6) alkyl, hydroxy-substituted (C_1-C_6) alkyl, (C_1-C_3) alkoxy-substituted (C_1-C_3) alkyl, phenyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, or a halogen atom;

and pharmaceutical salts and esters thereof.

39. The compound of Claim 38, wherein

R^1 , R^2 , and R^3 are defined as in Claim 1;



where R^4 is hydrogen;

R^5 is



where R^6 is hydrogen or (C_1-C_6) alkyl;

R^7 is phenyl optionally substituted with one or more of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, or a halogen atom;

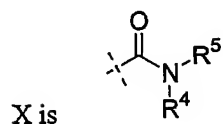
and pharmaceutical salts and esters thereof.

40. The compound of Claim 39, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, (C_1-C_6) alkyl sulfonyl, (C_1-C_6) alkyl sulfonyl-amino, (C_1-C_6) alkyl carbonyl-amino, (C_1-C_6) alkyl amino-carbonyl-amino, or phenyl;

R^3 is hydrogen, (C_1-C_6) alkyl, benzyl, chloro, or bromo;



where R⁴ is hydrogen;

R⁵ is



where R⁶ is hydrogen or (C₁-C₆)alkyl;

R⁷ is phenyl optionally substituted with one or more of (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or a halogen atom;

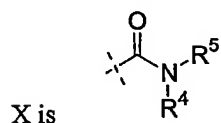
and pharmaceutical salts thereof.

41. The compound of Claim 40, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;



where R⁴ is hydrogen;

R⁵ is



where R⁶ is hydrogen or (C₁-C₆)alkyl;

R⁷ is phenyl optionally substituted with one or more of (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or a halogen atom;

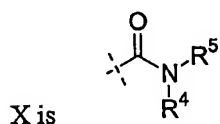
and pharmaceutical salts thereof.

42. The compound of Claim 41, wherein

5 R^1 and R^2 are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

10



where R^4 is hydrogen;

15

R^5 is



where R^6 is hydrogen or (C_1-C_6) alkyl;

20

R^7 is phenyl optionally substituted with one or more of (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, or a halogen atom;

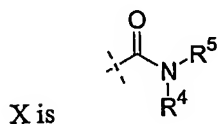
and pharmaceutical salts thereof.

43. The compound of Claim 42, wherein

25 R^1 and R^2 are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

30



where R⁴ is hydrogen;

R⁵ is



where R⁶ is hydrogen or methyl;

R⁷ is phenyl optionally substituted with one or more of trifluoromethyl, cyano, or a halogen atom;

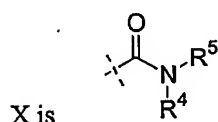
and pharmaceutical salts thereof.

44. The compound of Claim 1, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, (C₁-C₆)alkyl sulfonyl, (C₁-C₆)alkyl sulfonyl-amino, (C₁-C₆)alkyl carbonyl-amino, (C₁-C₆)alkyl amino-carbonyl-amino, or phenyl;

R³ is hydrogen or (C₁-C₆)alkyl;



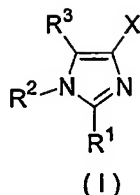
where R⁴ is hydrogen;

R⁵ is selected from

piperidin-4-yl, piperidin-3-yl, or pyrrolidin-3-yl, each of which may optionally be substituted on the nitrogen atom of the piperidine or pyrrolidine ring with (C₁-C₆)alkyl, hydroxy-substituted (C₁-C₆)alkyl, (C₁-C₃)alkoxy-substituted (C₁-C₃)alkyl, benzyl, or phenyl optionally substituted with one or more of (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy, nitro, or halogen;

and pharmaceutical salts and esters thereof.

45. A compound of Formula I,



wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, (C₁-C₆)alkyl carbonyl-amino, (C₁-C₆)alkyl amino-carbonyl-amino, or phenyl,

(C₂-C₆)alkyl,

cyclohexyl optionally substituted with (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or with one or more fluorine,

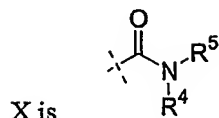
1- or 2-naphthyl optionally substituted with halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano,

benzyl optionally substituted on the phenyl ring with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano,

a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with fluorine, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano, and

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or phenyl, with the proviso that R² is not an unsubstituted 4-pyridyl or an unsubstituted 4-pyrimidinyl group;

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;

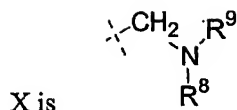


where R⁴ is hydrogen or (C₁-C₆)alkyl;

5 R⁵ is phenyl substituted with one or more (C₁-C₆)alkyl, hydroxy (C₁-C₆)alkyl, (C₁-C₆)alkoxy, phenyl, hydroxy, benzyloxy, trifluoromethyl, or halogen, or

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical,
optionally substituted with one or more (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or
10 trifluoromethyl,

or



15 where R⁸ is a hydrogen or (C₁-C₆)alkyl;

R⁹ is a (C₁-C₉)alkyl or (C₇-C₁₁)bicycloalkyl group, each of which is optionally substituted
with one or more of phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, or fluorine, or

20 benzyl in which the phenyl ring is optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or
halogen, or

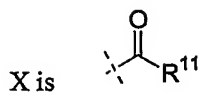
25 phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl
ring with one or more of a phenyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, or
halogen,

or

30 R⁸ and R⁹, together with the nitrogen atom to which they are attached, form a 5- to 10-
membered saturated or unsaturated heterocyclic radical optionally substituted with
one or more of (C₁-C₆)alkyl, benzyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy,

halogen, a 5- to 10-membered saturated or unsaturated heterocyclic radical; or
 phenyl optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy,
 benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen;

5 or



10 where R¹¹ is (C₂-C₉)alkyl optionally substituted with one or more phenyl, hydroxy,
 benzyloxy, (C₁-C₆)alkoxy, or fluorine,

phenyl in which the phenyl ring is optionally substituted with one or more of
 (C₁-C₆)alkyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro,
 or halogen,

15

benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which may
 be optionally substituted on one of the alkyl carbons with hydroxy, benzyloxy, or
 hydroxy (C₁-C₆)alkyl, and optionally substituted on the phenyl ring with halogen,
 (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy or nitro,
 20 or

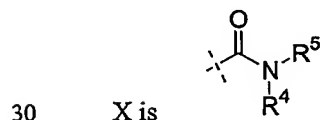
a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical;

and pharmaceutical salts and esters thereof.

25

46. The compound of Claim 45, wherein

R¹, R², and R³ are defined as in Claim 45;



where R⁴ is hydrogen or (C₁-C₆)alkyl;

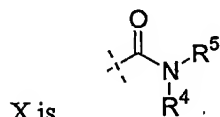
R^5 is phenyl substituted with one or more (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, (C_1-C_6) alkoxy, phenyl, hydroxy, benzyloxy, trifluoromethyl, or halogen, or

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical,
optionally substituted with one or more (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or
trifluoromethyl;

and pharmaceutical salts and esters thereof.

47. The compound of Claim 46, wherein

R^1 , R^2 , and R^3 are defined as in Claim 45;



where R^4 is hydrogen or (C_1-C_6) alkyl;

R^5 is phenyl substituted with one or more (C_1-C_6) alkyl, (C_1-C_6) alkoxy, hydroxy, trifluoromethyl, or halogen, or

a 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, or 2-pyrazinyl, optionally substituted with one or more (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or trifluoromethyl;

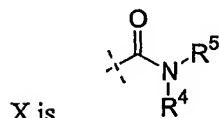
and pharmaceutical salts and esters thereof.

48. The compound of Claim 47, wherein

R^1 and R^2 are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, (C_1-C_6) alkyl carbonyl-amino, (C_1-C_6) alkyl amino-carbonyl-amino, or phenyl;

R^3 is hydrogen, (C_1-C_6) alkyl, benzyl, chloro, or bromo;



where R⁴ is hydrogen or (C₁–C₆)alkyl;

R⁵ is phenyl substituted with one or more (C₁–C₆)alkyl, (C₁–C₆)alkoxy, hydroxy,
trifluoromethyl, or halogen, or

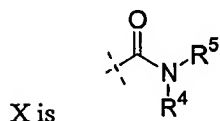
a 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, or 2-pyrazinyl, optionally substituted with one or more (C₁–C₆)alkyl, (C₁–C₆)alkoxy, or trifluoromethyl;

and pharmaceutical salts and esters thereof.

49. The compound of Claim 48, wherein

R¹ and R² are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, (C₁–C₆)alkyl, benzyl, chloro, or bromo;



where R⁴ is hydrogen or (C₁–C₆)alkyl;

R⁵ is phenyl substituted with one or more (C₁–C₆)alkyl, (C₁–C₆)alkoxy, hydroxy,
trifluoromethyl, or halogen, or

a 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, or 2-pyrazinyl, optionally substituted with one or more (C₁–C₆)alkyl, (C₁–C₆)alkoxy, or trifluoromethyl;

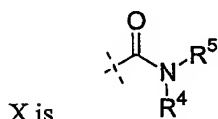
and pharmaceutical salts and esters thereof.

50. The compound of Claim 49, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁–C₆)alkyl, (C₁–
5 C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



10 where R⁴ is hydrogen or (C₁–C₆)alkyl;

R⁵ is phenyl substituted with one or more (C₁–C₆)alkyl, (C₁–C₆)alkoxy, hydroxy,
trifluoromethyl, or halogen, or

15 a 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, or 2-
pyrazinyl, optionally substituted with one or more (C₁–C₆)alkyl, (C₁–C₆)alkoxy, or
trifluoromethyl;

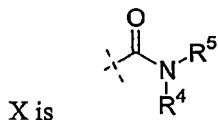
and pharmaceutical salts and esters thereof.

51. The compound of Claim 50, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁–C₆)alkyl, (C₁–
25 C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



30 where R⁴ is hydrogen;

R^5 is phenyl substituted with one or more (C_1-C_6) alkyl, (C_1-C_6) alkoxy, hydroxy, trifluoromethyl, or halogen;

and pharmaceutical salts and esters thereof.

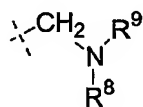
5

52. The compound of Claim 45, wherein

R^1 , R^2 , and R^3 are defined as in Claim 45;

10

X is



where R^8 is a hydrogen or (C_1-C_6) alkyl;

15

R^9 is a (C_1-C_9) alkyl or (C_7-C_{11}) bicycloalkyl group, each of which is optionally substituted with one or more of phenyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, or fluorine, or

benzyl in which the phenyl ring is optionally substituted with one or more of (C_1-C_6) alkyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, or halogen, or

20

phenyl, benzocyclohexyl or benzocyclopentyl optionally substituted on the phenyl ring with one or more of a phenyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, or halogen,

or

25

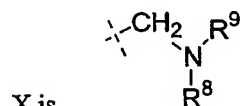
R^8 and R^9 , together with the nitrogen atom to which they are attached, form a 5- to 10-membered saturated or unsaturated heterocyclic radical optionally substituted with one or more of (C_1-C_6) alkyl, benzyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, halogen, a 5- to 10-membered saturated or unsaturated heterocyclic radical; or phenyl optionally substituted with one or more of (C_1-C_6) alkyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, nitro, or halogen;

30

and pharmaceutical salts and esters thereof.

53. The compound of Claim 52, wherein

R¹, R², and R³ are defined as in Claim 45;



where R⁸ is a hydrogen or (C₁-C₆)alkyl;

R⁹ is a (C₁-C₉)alkyl, optionally substituted with one or more of hydroxy or fluorine, or

benzyl in which the phenyl ring is optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or halogen;

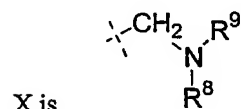
and pharmaceutical salts and esters thereof.

54. The compound of Claim 53, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, (C₁-C₆)alkyl carbonyl-amino, (C₁-C₆)alkyl amino-carbonyl-amino, or phenyl;

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;



where R⁸ is a hydrogen or (C₁-C₆)alkyl;

R⁹ is a (C₁-C₉)alkyl, optionally substituted with one or more of hydroxy or fluorine, or

benzyl in which the phenyl ring is optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or halogen,

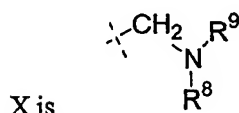
and pharmaceutical salts and esters thereof.

55. The compound of Claim 54, wherein

5 R^1 and R^2 are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, (C_1-C_6) alkyl, benzyl, chloro, or bromo;

10



where R^8 is a hydrogen or (C_1-C_6) alkyl;

15 R^9 is a (C_1-C_9) alkyl, optionally substituted with one or more of hydroxy or fluorine, or

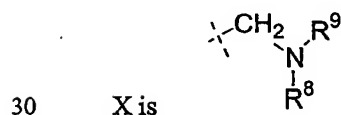
benzyl in which the phenyl ring is optionally substituted with one or more of (C_1-C_6) alkyl, hydroxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, or halogen;

20 and pharmaceutical salts and esters thereof.

56. The compound of Claim 55, wherein

25 R^1 and R^2 are identical or different and are selected from
a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



where R^8 is a hydrogen or (C_1-C_6) alkyl;

R^9 is a (C_1-C_9) alkyl, optionally substituted with one or more of hydroxy or fluorine, or

benzyl in which the phenyl ring is optionally substituted with one or more of (C_1-C_6) alkyl, hydroxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, or halogen;

5

and pharmaceutical salts and esters thereof.

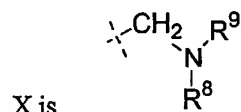
57. The compound of Claim 56, wherein

10

R^1 and R^2 are identical or different and are selected from a phenyl group optionally substituted with one or more halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, trifluoromethyl, or cyano;

R^3 is hydrogen, methyl, ethyl, n-propyl, or n-butyl;

15



where R^8 is a hydrogen or (C_1-C_6) alkyl;

20

R^9 is cyclohexyl or 2-hydroxycyclohexyl, or

benzyl in which the phenyl ring is optionally substituted with one or more of (C_1-C_6) alkyl, hydroxy, (C_1-C_6) alkoxy, trifluoromethyl, cyano, or halogen;

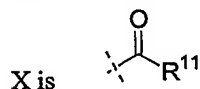
25

and pharmaceutical salts and esters thereof.

58. The compound of Claim 45, wherein

R^1 , R^2 , and R^3 are defined as in Claim 45;

30



where R^{11} is (C_2-C_9) alkyl optionally substituted with one or more phenyl, hydroxy, benzyloxy, (C_1-C_6) alkoxy, or fluorine,

phenyl, optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy, benzyloxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, or halogen,

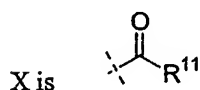
benzyl, 2-phenyl-ethyl, benzocyclohexyl or benzocyclopentyl, each of which may be optionally substituted on one of the alkyl carbons with hydroxy, benzyloxy, or hydroxy (C₁-C₆)alkyl, and optionally substituted on the phenyl ring with halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, hydroxy, benzyloxy or nitro, or

a 5- to 10-membered aromatic monocyclic or bicyclic heterocyclic radical;

and pharmaceutical salts and esters thereof.

59. The compound of Claim 58, wherein

R¹, R², and R³ are defined as in Claim 45;



where R¹¹ is (C₂-C₉)alkyl optionally substituted with one or more phenyl, hydroxy, (C₁-C₆)alkoxy, or fluorine,

phenyl, optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or halogen;

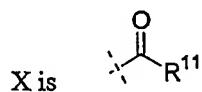
and pharmaceutical salts and esters thereof.

60. The compound of Claim 59, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, cyano, nitro, (C₁-C₆)alkyl carbonyl-amino, (C₁-C₆)alkyl amino-carbonyl-amino, or phenyl;

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;



5 where R¹¹ is (C₂-C₉)alkyl optionally substituted with one or more phenyl, hydroxy, (C₁-C₆)alkoxy, or fluorine,

phenyl, optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or halogen;

10

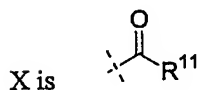
and pharmaceutical salts and esters thereof.

61. The compound of Claim 60, wherein

15 R¹ and R² are identical or different and are selected from a phenyl group optionally substituted with one or more halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, (C₁-C₆)alkyl, benzyl, chloro, or bromo;

20



where R¹¹ is (C₂-C₉)alkyl optionally substituted with one or more phenyl, hydroxy, (C₁-C₆)alkoxy, or fluorine,

25

phenyl, optionally substituted with one or more of (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, trifluoromethyl, cyano, or halogen;

and pharmaceutical salts and esters thereof.

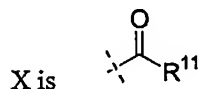
30

62. The compound of Claim 61, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, trifluoromethyl, or cyano;

R³ is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



where R¹¹ is (C₂–C₉)alkyl optionally substituted with one or more phenyl, hydroxy, (C₁–C₆)alkoxy, or fluorine,

10
phenyl, optionally substituted with one or more of (C₁–C₆)alkyl, hydroxy, (C₁–C₆)alkoxy, trifluoromethyl, cyano, or halogen;

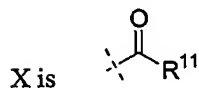
and pharmaceutical salts and esters thereof.

15
63. The compound of Claim 62, wherein

R¹ and R² are identical or different and are selected from

a phenyl group optionally substituted with one or more halogen, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, trifluoromethyl, or cyano;

20
R³ is hydrogen, methyl, ethyl, n-propyl, or n-butyl;



where R¹¹ is (C₂–C₉)alkyl,

phenyl, optionally substituted with one or more of (C₁–C₆)alkyl, hydroxy, (C₁–C₆)alkoxy, trifluoromethyl, cyano, or halogen;

30
and pharmaceutical salts and esters thereof.

64. A compound selected from the group consisting of:

1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-(4-fluorophenyl)-4-piperidinol;
1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-(4-chlorophenyl)-4-piperidinol;
1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-[3-(trifluoromethyl)phenyl]-4-piperidinol;
1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-(4-trifluoromethoxyphenyl)-4-piperidinol;
1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-(3-fluorophenyl)-4-piperidinol;
1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-1H-imidazol-4-yl}carbonyl}-4-(3-chlorophenyl)-4-piperidinol;
1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-(3-fluoro-4-chlorophenyl)-4-piperidinol;
1-{{2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl}carbonyl}-4-[3-(trifluoromethoxy)phenyl]-4-piperidinol;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[1-(2-pyridinyl)-4-piperidinyl]-1H-imidazole-4-carboxamide;
[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl](cyclohexyl)methanone;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-(4-pyridinyl)-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[3-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
N'-[2-chloro-4-(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-chloro-2-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
N'-[4-chloro-2-methylphenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
N'-(2,4-dichlorophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
N'-[2,4-bis(trifluoromethyl)phenyl]-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;

N'-(2-chloro-4-cyanophenyl)-2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carbohydrazide;
1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide;
1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-1H-imidazole-4-carboxamide;
1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-butyl-1H-imidazole-4-carboxamide;
1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;
1-(4-bromophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;
1-(4-chlorophenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-methyl-1H-imidazole-4-carboxamide;
1-(4-isopropylphenyl)-2-(2-chlorophenyl)-N-(1-piperidinyl)-5-ethyl-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-hexahydrocyclopenta[c]pyrrol-2(1H)-yl-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N'-[4-(trifluoromethyl)phenyl]-1H-imidazole-4-carbohydrazide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-N-[(1S,2S)-2-hydroxycyclopentyl]-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
2-(2-chlorophenyl)-1-(4-chlorophenyl)-5-propyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(1S,2S)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(1R,2R)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;
1-(4-bromophenyl)-2-(2-chlorophenyl)-5-ethyl-N-[(cis)-2-hydroxycyclohexyl]-1H-imidazole-4-carboxamide;

4-(4-{[1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile; and
4-(4-{[2-(2-chlorophenyl)-1-(4-chlorophenyl)-1H-imidazol-4-yl]carbonyl}-1-piperazinyl)benzonitrile.

65. A pharmaceutical composition comprising an effective amount of a compound of claim 1,
or a pharmaceutically acceptable salt or ester thereof, in combination with a
pharmaceutically acceptable carrier.

66. A pharmaceutical composition comprising an effective amount of a compound of claim
45, or a pharmaceutically acceptable salt or ester thereof, in combination with a
pharmaceutically acceptable carrier.

67. A pharmaceutical composition comprising an effective amount of a compound of claim
64, or a pharmaceutically acceptable salt or ester thereof, in combination with a
pharmaceutically acceptable carrier.

68. A pharmaceutical composition comprising an effective amount of a compound of claim 1,
or a pharmaceutically acceptable salt or ester thereof, in combination with a
pharmaceutically acceptable carrier and one or more hypoglycemic agents.

69. The pharmaceutical composition of claim 68, wherein said hypoglycemic agent is selected
from the group consisting of insulin, biguanidines, sulfonylureas, insulin secretagogues, α -
glycosidase inhibitors, and β_3 -adrenoreceptor agonists.

70. A pharmaceutical composition comprising an effective amount of a compound of claim
45, or a pharmaceutically acceptable salt or ester thereof, in combination with a
pharmaceutically acceptable carrier and one or more hypoglycemic agents.

71. The pharmaceutical composition of claim 70, wherein said hypoglycemic agent is selected
from the group consisting of insulin, biguanidines, sulfonylureas, insulin secretagogues, α -
glycosidase inhibitors, and β_3 -adrenoreceptor agonists.

72. A pharmaceutical composition comprising an effective amount of a compound of claim
64, or a pharmaceutically acceptable salt or ester thereof, in combination with a

pharmaceutically acceptable carrier and one or more hypoglycemic agents.

- 5 73. The pharmaceutical composition of claim 72, wherein said hypoglycemic agent is selected from the group consisting of insulin, biguanidines, sulfonylureas, insulin secretagogues, α -glycosidase inhibitors, and β_3 -adrenoreceptor agonists.
- 10 74. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.
- 15 75. A pharmaceutical composition comprising an effective amount of a compound of claim 45, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.
- 20 76. A pharmaceutical composition comprising an effective amount of a compound of claim 64, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.
- 25 77. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.
- 30 78. A pharmaceutical composition comprising an effective amount of a compound of claim 45, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.
- 35 79. A pharmaceutical composition comprising an effective amount of a compound of claim

64, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

5

80. A composition comprising an effective amount of a compound of claim 1, or a salt or ester thereof, in combination with an inert carrier.

10

81. A composition comprising an effective amount of a compound of claim 45, or a salt or ester thereof, in combination with an inert carrier.

82. A composition comprising an effective amount of a compound of claim 64, or a salt or ester thereof, in combination with an inert carrier.

15

83. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.

20

84. The method of claim 83, wherein said obesity-related disorders include dyslipidemia, hypertriglyceridemia, hypertension, diabetes, Syndrome X, atherosclerotic disease, cardiovascular disease, cerebrovascular disease, peripheral vessel disease, cholesterol gallstones, cancer, menstrual abnormalities, infertility, polycystic ovaries, osteoarthritis, and sleep apnea.

25

85. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45.

30

86. The method of claim 85, wherein said obesity-related disorders include dyslipidemia, hypertriglyceridemia, hypertension, diabetes, Syndrome X, atherosclerotic disease, cardiovascular disease, cerebrovascular disease, peripheral vessel disease, cholesterol gallstones, cancer, menstrual abnormalities, infertility, polycystic ovaries, osteoarthritis, and sleep apnea.

35

87. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a

compound of claim 64.

- 5 88. The method of claim 87, wherein said obesity-related disorders include dyslipidemia, hypertriglyceridemia, hypertension, diabetes, Syndrome X, atherosclerotic disease, cardiovascular disease, cerebrovascular disease, peripheral vessel disease, cholesterol gallstones, cancer, menstrual abnormalities, infertility, polycystic ovaries, osteoarthritis, and sleep apnea.
- 10 89. A method of regulating appetite and food intake comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.
90. A method of regulating appetite and food intake comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45.
- 15 91. A method of regulating appetite and food intake comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64.
92. A method of treating bulimia comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.
- 20 93. A method of treating bulimia comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45.
94. A method of treating bulimia comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64.
- 25 95. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1 in combination with one or more hypoglycemic agents.
- 30 96. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45 in combination with one or more hypoglycemic agents.
- 35 97. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a

compound of claim 64 in combination with one or more hypoglycemic agents.

5 98. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1 in combination with one or more agents that modulate digestion and/or metabolism.

10 99. The method of claim 98, wherein said agents that modulate digestion and/or metabolism include agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

100. The method of claim 99, wherein said agents that modulate digestion and/or metabolism include β_3 -adrenoreceptor agents.

15 101. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45 in combination with one or more agents that modulate digestion and/or metabolism.

20 102. The method of claim 101, wherein said agents that modulate digestion and/or metabolism include agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

25 103. The method of claim 102, wherein said agents that modulate digestion and/or metabolism include β_3 -adrenoreceptor agents.

30 104. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64 in combination with one or more agents that modulate digestion and/or metabolism.

35 105. The method of claim 104, wherein said agents that modulate digestion and/or metabolism include agents that modulate thermogenesis, lipolysis, gut motility, fat absorption, and satiety.

106. The method of claim 105, wherein said agents that modulate digestion and/or metabolism

include β_3 -adrenoreceptor agents.

- 5 107. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1 in combination with one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.
- 10 108. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45 in combination with one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.
- 15 109. A method of treating obesity and obesity-related disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64 in combination with one or more agents selected from the group consisting of HMG CoA reductase inhibitor, bile acid binding agent, fibric acid derivative, and agent that regulates hypertension.
- 20 110. A method of treating CNS disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.
- 25 111. A method of treating cognition and memory disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.
- 30 112. A method of treating substance or behavioral addiction comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 1.
113. A method of treating CNS disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45.
- 35 114. A method of treating cognition and memory disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a

compound of claim 45.

- 5 115. A method of treating substance or behavioral addiction comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 45.
116. A method of treating CNS disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64.
- 10 117. A method of treating cognition and memory disorders comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64.
- 15 118. A method of treating substance or behavioral addiction comprising the step of administering to a patient in need thereof a pharmaceutically effective amount of a compound of claim 64.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/30545

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D233/90 C07D401/04 C07D405/04 C07D409/04 C07D413/04
A61K31/415 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | WO 01 40207 A (SIERRA MICHAEL LAWRENCE ;GLAXO GROUP LTD (GB)) 7 June 2001 (2001-06-07) claims; examples | 1-118 |
| Y | WO 00 69849 A (ORTHO MCNEIL PHARM INC) 23 November 2000 (2000-11-23) page 32 -page 42 | 1-118 |
| P,Y | WO 02 064136 A (CHUGAI PHARMACEUTICAL CO LTD ;CHEN MI (US); CHENG JIE FEI (US); HU) 22 August 2002 (2002-08-22) claims; examples 22,23 | 1-118 |
| Y | WO 98 27065 A (ONTOGEN CORP) 25 June 1998 (1998-06-25) page 73 -page 74; claims; examples | 1-118 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the International search

4 March 2003

Date of mailing of the international search report

17/03/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Menegaki, F

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/30545

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 88-118 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International on patent family members

International Application No

PCT/US 02/30545

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|--|--|
| WO 0140207 | A | 07-06-2001 | AU 2003001 A BR 0016067 A CZ 20021903 A3 WO 0140207 A1 EP 1244642 A1 NO 20022467 A TR 200201473 T2 US 6518290 B1 | 12-06-2001 06-08-2002 15-01-2003 07-06-2001 02-10-2002 26-07-2002 23-09-2002 11-02-2003 |
| WO 0069849 | A | 23-11-2000 | AU 4690600 A EP 1177188 A1 WO 0069849 A1 US 6291476 B1 US 2002058816 A1 | 05-12-2000 06-02-2002 23-11-2000 18-09-2001 16-05-2002 |
| WO 02064136 | A | 22-08-2002 | WO 02058690 A2 WO 02064136 A2 | 01-08-2002 22-08-2002 |
| WO 9827065 | A | 25-06-1998 | US 5770620 A WO 9827065 A1 AU 740425 B2 AU 1566797 A AU 7735896 A EP 0833629 A2 EP 0946518 A1 JP 2001506997 T WO 9708934 A2 US 5753687 A AU 713863 B2 CA 2224874 A1 JP 11508919 T US 6150532 A US 6388076 B1 US 5965558 A US 2002183518 A1 | 23-06-1998 25-06-1998 01-11-2001 15-07-1998 27-03-1997 08-04-1998 06-10-1999 29-05-2001 13-03-1997 19-05-1998 09-12-1999 13-03-1997 03-08-1999 21-11-2000 14-05-2002 12-10-1999 05-12-2002 |

CORRECTED VERSION

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
15 May 2003 (15.05.2003)

PCT

(10) International Publication Number
WO 2003/040107 A1

(51) International Patent Classification⁷: C07D 233/90,
401/04, 405/04, 409/04, 413/04, A61K 31/415, A61P 3/04

(21) International Application Number:
PCT/US2002/030545

(22) International Filing Date:
24 September 2002 (24.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/324,473 24 September 2001 (24.09.2001) US

(71) Applicant (for all designated States except US): BAYER
PHARMACEUTICALS CORPORATION [US/US];
400 Morgan Lane, West Haven, CT 06516 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): SMITH, Roger,
A. [US/US]; 65 Winterhill Road, Madison, CT 06443
(US). O'CONNOR, Stephen, J. [US/US]; 977 Little
Meadow Road, Guilford, CT 06437 (US). WIRTZ,
Stephan-Nicholas [DE/DE]; Briller Strasse 40, 42105
Wuppertal (DE). WONG, Wal, C. [US/US]; 314 Aspen
Glen Drive, Hamden, CT 06518 (US). CHOI, Soongyu
[KR/US]; 44 Jamestown Road, Trumbull, CT 06611 (US).
KLUENDER, Harold, C. E. [US/US]; 27 Academy
Road, Trumbull, CT 06611 (US). SU, Ning [CN/US]; 121
October Hill Road, Hamden, CT 06518 (US). WANG,
Gan [CN/US]; 5 Cassella Drive, Wallingford, CT 06492
(US). ACHEBE, Furahi [US/US]; 10 Woodland Street,
West Haven, CT 06516 (US). YING, Shihong [CN/US];
280 Bittersweet Road, Orange, CT 06477 (US).

(74) Agents: GREENMAN, Jeffrey, M. et al.; Bayer Pharma-
ceuticals Corporation, 400 Morgan Lane, West Haven, CT
06516 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL,
SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG,
KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH,
CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for all designations

Published:

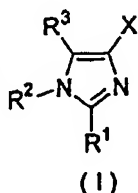
- with international search report

(48) Date of publication of this corrected version:
29 July 2004

(15) Information about Correction:
see PCT Gazette No. 31/2004 of 29 July 2004, Section II

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZOLE-4-CARBOXAMIDE DERIVATIVES, PREPARATION AND USE THEREOF FOR TREATMENT OF
OBESITY



(57) Abstract: This invention relates to substituted imidazole derivatives of formula I, which have been found
to suppress appetite and induce weight loss. The invention also provides methods for synthesis of the com-
pounds, pharmaceutical compositions comprising the compounds, and methods of using such compositions
for inducing weight loss and treating obesity and obesity-related disorders.